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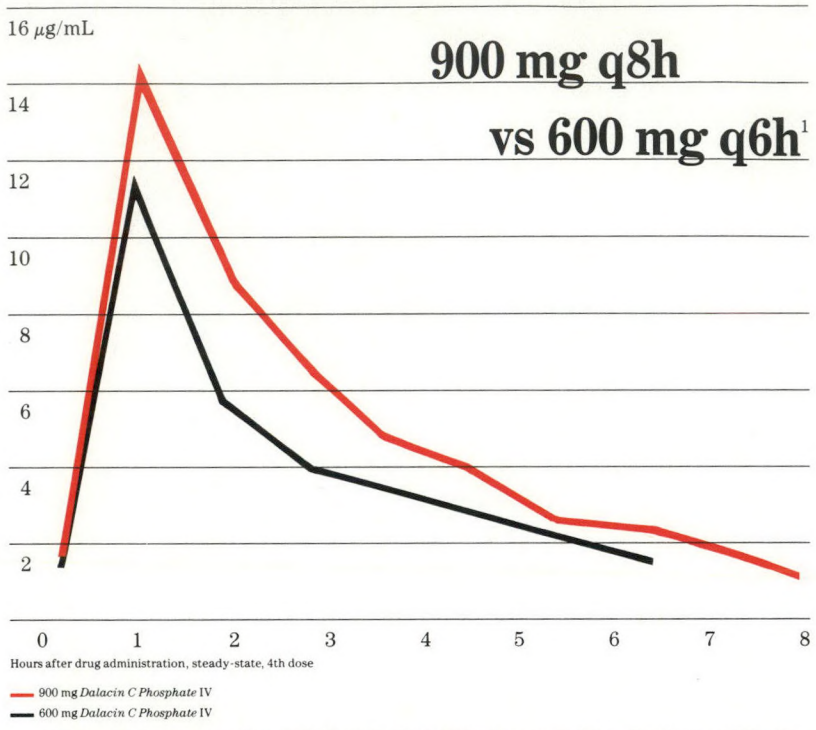

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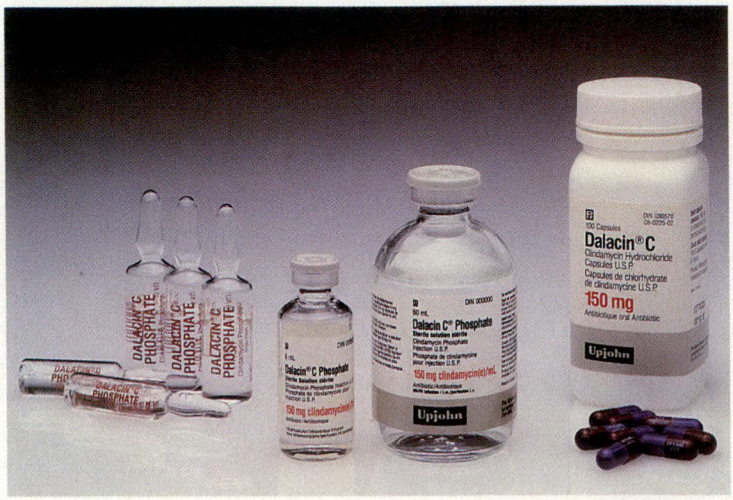

1. Adapted from: Townsend R., Pharmacokinetic Comparison of Three Clindamycin Phosphate Dosing Schedules. Drug Intelligence and Clinical Pharmacy, 1987;21:279-81.
2. Rowland B.J., Erricsson C.D.: American Journal of Surgery 1984, 148 p. 791-795.
3. Ericsson Booklet – Data on File

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Cover picture

A randomly organized network of collagen fibril bundles is seen on the external surface of a virgin bovine internal mammary artery graft prosthesis. Such a structure provides anchorage for proliferating fibrous tissue during the healing phase after implantation (see article on pages 180 to 187).

Peritoneal Carcinomatosis: the Role of Debulking Procedures

Peter R. Knight, MB, ChB, ChM, FRCSC, FACS, FRCS

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During the 3 days of his stay in Southern Ontario, Dr. Paul Sugarbaker, the 1988 Du Pont visiting professor, conducted grand rounds at the Brantford General Hospital, McMaster University Medical Centre and the Stratford General Hospital and also addressed the annual meeting of the Southern Ontario Surgical Society. His paper on the surgical treatment of peritoneal carcinomatosis appears in this issue of the Journal (pages 164 to 170).

The concept of debulking tumours to give chemotherapeutic agents better exposure to residual tumour cells is, of course, not new. For many years, gynecologists have used omentectomy and other debulking procedures in combination with various chemotherapeutic regimens in the treatment of carcinoma of the ovary.

Pseudomyxoma peritonei is a lesion of low-grade malignancy that does not metastasize but recurs locally. Repeated removal of these locally recurring tumour masses in the peritoneal cavity is usually associated with long-term survival. Removing such masses with laser or ball-tipped cautery may well be a reasonable approach.

For general surgeons, accustomed to the ravages wrought by recurrent and metastatic carcinoma of the rectum and colon, this approach may cause raised eyebrows. Such patients usually present with extensive seeding of the peritoneum and bowel surfaces and neoplastic adhesions so vicious that the abdominal contents are solidly stuck together with multiple areas of obstruction. The prospect of freeing these peritoneal plaques of carcinoma and disentangling and freeing multiple loops of bowel by ball-tipped cautery on high voltage may make even the most aggressive,

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

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optimistic surgeon pale. The addition to this of excision of transverse colon, spleen and terminal ileum, the ligament of Treitz and the greater and lesser omentum, makes the procedure even more overwhelming.

The role of intraperitoneal chemotherapy[1] has evolved from the finding that patients who had ovarian cancer and ascites had a high rate of chemotherapy-induced myelosuppression when chemotherapy was given intravenously. It was found that the drugs accumulated in the ascitic fluid and, eventually, the ascitic fluid concentration of the drug exceeded the plasma concentration. The ascitic fluid then provided a slow release form of the drug into the plasma, slurring the terminal disappearance curve. It was concluded that a diffusion barrier associated with the peritoneum was the responsible factor.

The problem of poor distribution of chemotherapeutic agents instilled into the peritoneal cavity is obvious in patients with bulky disease and multiple adhesions. This distribution can be shown radiologically by adding Hypaque to the fluid introduced into the peritoneal cavity. The distribution of dye-containing fluid in ovarian cancer patients is known to be excellent.[1] For patients who have metastatic colonic and rectal carcinoma with dense adhesions and matting of the loops of bowel, the distribution is likely to be poor. The benefits of local chemotherapy may thus be lost. Dr. Sugarbaker makes no comment on the distribution pattern of his chemotherapeutic fluid.

The ability of intraperitoneally administered drugs to penetrate solid intra-abdominal tumour masses directly has not been shown experimentally for most anti-cancer drugs. However, a mathematical model defined by a set of non-linear partial differential equations has predicted 5-fluorouracil tumour penetration to a depth of 600 μm. This represents a thickness of approximately 50 to 60 cells.[2] Thus, intraperitoneal therapy would appear to be limited in usefulness to tumour nodules of only a few millimetres in diameter. 5-fluorouracil is absorbed from the peritoneal cavity, thus the tumour would also be exposed to chemotherapeutic cytotoxicity via its capillary blood supply. The vascularity of the deeper parts of large, bulky tumours is poor, limiting the availability of chemotherapeutic levels of cytotoxic drugs within large tumour masses. For these reasons, debulking is a rational approach if it can be achieved, even though after such a procedure adhesions are very likely to reform, preventing local access of chemotherapeutic agents to the debulked tumour masses.

The mortality and morbidity associated with debulking is obviously high and many patients who undergo these procedures are probably poor candidates in terms of nutrition and healing capability. Their immune competence to deal with infection is also probably depressed. If satisfactory debulking can be achieved, then a course of chemotherapy given intraperitoneally, as outlined by Dr. Sugarbaker, must require a robust recipient indeed. Such an undertaking is obviously not suitable for anything but well-equipped research departments with trained oncologists and with patient and aggressive surgeons who are prepared to embark upon prolonged surgical "tours de force" as part of a research study. The aim of any procedure should be to prolong life which is of good quality. Patients such as Sugarbaker describes run a high risk of tumour recurrence, and the masses may never be completely or successfully removed. This raises the questions, How much of their remaining lives will these patients spend in hospital undergoing repeated surgical and oncologic treatment? and Can such a program really achieve our desired aim?

On the other hand, progress is made through people with courage and the willingness to tilt at windmills and challenge problems from which others turn. From such beginnings, new pathways may appear, and it is good to realize there are people prepared to undertake what appears impossible. From such beginnings the impossible may become a reality.

The area covered by Dr. Sugarbaker in his Du Pont Lecture is just part of a program he is undertaking. Most of us must await his ongoing results and achievements before embarking on what must be a hazardous and rocky path for both surgeon and patient.

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CORRESPONDENCE

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

Treatment of Genital Herpes: an Option

To the editors. A number of well-documented articles on the diagnosis and management of genital herpes have appeared recently,[1-6] the treatment of both acute and chronic herpatic lesions generally involving the use of acyclovir. I would like to suggest a further treatment option, one that has been used effectively at the University Health Services in Edmonton for a number of years.

Liquid nitrogen as a freezing procedure has met with excellent patient acceptance and provided amazing clinical healing within 1 week of treatment, whether used for a primary outbreak of herpes or for recurrent lesions. The liquid nitrogen is applied with a cotton-tipped applicator to the involved area, no matter how extensive, to freeze the entire thickness of the lesions. Patients who have widespread involvement of the vulvar area and are obviously in severe distress are most grateful for the immediate relief and rapid healing. No other medication is required.

This method is also used in the treatment of condyloma acuminatum, molluscum contagiosum and ulcerative lesions of the vulva (e.g., Lipschütz ulcers).

I hope this alternative treatment for genital herpes will prove helpful to others who must deal with this distressing condition.

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Primary Omental Torsion

To the editors. I read with interest Appleby's report on primary omental torsion in the January 1989 issue (page 7). Having seen a number of these cases in my surgical career, I would like to add to Appleby's description.

First, these patients usually do not present with nausea and vomiting, and the abdominal pain and tenderness seem disproportionate to their generalized symptoms. Second, most cases of primary omental torsion that I have seen are associated with an indirect inguinal hernia on the right side. These are noted in one of the classic descriptions of the condition.[1]

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Meatal-Based Tubularized Skin Flap For Distal Hypospadias Repair

M. Gleave, MD; H.W. Johnson, MD, FRCSC; G.U. Coleman, MD, FRCSC; M.G. McLoughlin, MD, FRCSC

Distal or anterior hypospadias accounts for approximately 70% of all cases of hypospadias, including those in which the urethral meatus opens proximal to its normal position in either a glanular, coronal or subcoronal position. When possible, we use a meatal advancement and glanuloplasty.[1] However, when the urethral meatus is either too proximal or is associated with a ventral chordee, this procedure will not produce the best results. Our choice in these circumstances is a modified Mustardé procedure,[2] using a meatal-based tubularized skin flap.

Patients

Since 1984, we have treated 40 boys for correction of distal penile hypospadias using a meatal-based tubularized skin flap. In 25, the repair was the primary treatment, and in 15, previous attempts (ranging from two to five procedures) at repair had failed.

The group who underwent primary repair ranged in age from 1 to 5 years. We prefer to operate when the boys are between 12 and 18 months of age after a 1-week course of androgens. The 15 boys who had revision repairs ranged in age from 5 to 15 years.

Surgical Procedure

A suture of 3-0 silk is placed through the glans and secured to the drapes cephalad. After the meatus has been sounded to 12F, a rectangular skin flap is outlined proximal to the urethral meatus (Fig. 1). The width of the flap determines the urethral circumference and is approximately one-third the circumference of the penile shaft (12 to 14 mm). The length is determined by the distance of the meatus from the tip of the glans. Any chordee between the corona and the meatus is divided completely before the proximal limit of the flap is marked, because some proximal migration of the meatus may occur as the penis is straightened. Saline erections are used to aid in the excision of the chordee if necessary.

The flap is then incised sharply down to Buck's fascia and undermined distally to the urethral meatus. The base of the flap now lies at the urethral meatus. The flap is tubularized (Fig. 2) into the neourethra over a no. 8 feeding tube or 10F Silastic stent with running 6-0 polyglycolic acid sutures. This single suture line is buried facing dorsally away from other surface suture lines.

After the glans has been infiltrated with 1 in 200 000 epinephrine, the neourethra is extended to the tip of the glans in one of two ways. If the glans is flat, a glanular tunnel

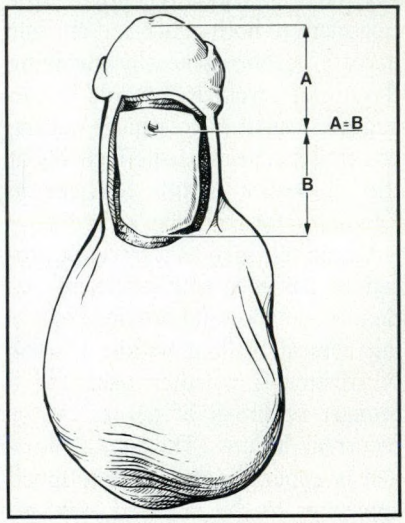

FIG. 1. Rectangular skin flap is 12 to 14 mm wide and length is equal to distance of meatus from tip of glans.

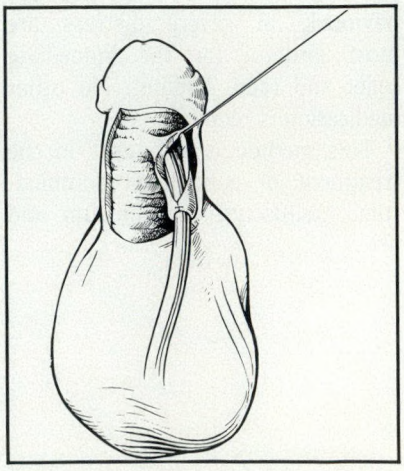

FIG. 2. Tubularization of skin flap over 10F Silastic tube.

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is created between the ventral glans and underlying distal corpora (18 patients) (Fig. 3a). If a ventral groove is present, then glanular flaps are raised (22 patients) and sutured over the neourethra with interrupted mattress sutures of 6-0 polyglycolic acid suture material (Fig. 3b).

Byars' flaps are then raised from the dorsal hood of foreskin and wrapped ventrally to cover the ventral defect (Fig. 4). A 10F silicone stent or Silastic catheter is placed for 5 to 7 days. The penis is wrapped in a cling compression dressing for 48 hours.

Results

The complication rate in boys who had primary repair was low. Two had small fistulas, one of them in association with a meatal stenosis. Both underwent a single surgical repair of the fistulas on a day-care basis with good results.

The 15 boys who had revision repairs did not fare as well. Five (33%) had fistulas, associated with meatal stenosis in three. One of the five had a wound infection that likely contributed to the fistula formation. All five had the fistulas and stenoses corrected on a day-care basis, although one required a second subsequent fistula repair.

Two boys required a day-care procedure to remove redundant skin tags.

Overall, nine patients (22.5%) required additional surgical procedures, all carried out on a day-care basis. No significant difference in complications was seen between the glanular tunnel technique and the flap technique.

The early functional and cosmetic results were good in 38 (95%) of the boys. They had a good urinary stream, straight erections and a glanular meatus. In two boys, these aims were not achieved; both complained of a deflected or splayed urinary stream.

Discussion

Several single-stage procedures to repair distal hypospadias and produce a meatus at the tip of the glans have been described. When meatal advancement and glanuloplasty are not applicable, we like to use a meatal-based tubularized skin flap, initially described by Mustardé[3] and later modified by Belman.[2] Other options include the Mathieu[4] or Horton–Devine[5] flip-flap procedures, various mobilized vascular flaps[6,7] or free skin grafts.[8] The last two are usually reserved for mid-penile or proximal hypospadias. The flip-flap procedures cannot be performed in one stage if there is an associated chordee, but meatal-based tubularized flaps can be used as a single-stage procedure in distal to mid-penile hypospadias, with or without chordee.

The low incidence of complications in primary repairs and the overall good functional and cosmetic results in 38 of the 40 boys reaffirms the effectiveness of the modified Mustardé procedure reported by others.[4,9] The higher complication rate associated with secondary or revision repairs (33%) results from mobilizing flaps with

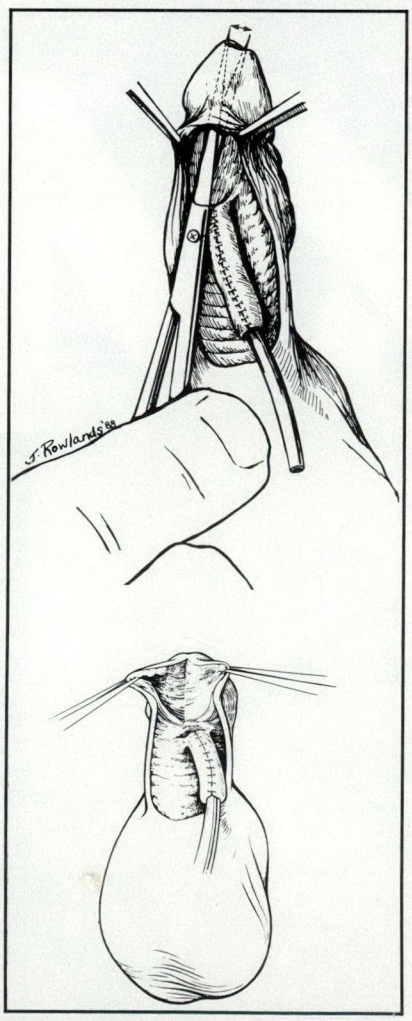

FIG. 3. Extension of tubularized flap to glanular tip via glanular tunnel (top) or by raising glanular flaps (bottom).

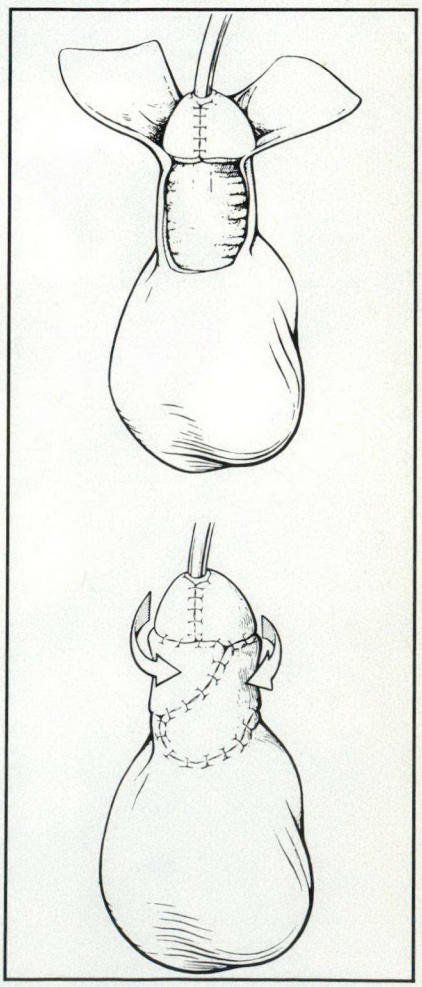

FIG. 4. Covering ventral defect with Byars' flaps.

compromised blood supply from previous operations. Despite this, a good final result was still obtained in 13 of these 15 problem patients.

The Mustardé meatal-based tubularized skin flap produces comparable results to other procedures used in the repair of mid-penile to distal hypospadias. The advantages include some flexibility in constructing the glanular course of the neourethra (flaps versus tunnel), creation of a neourethra with a single suture line that abuts the corpora dorsally to reduce the risk of fistulization and the ability to excise associated chordee allowing a single-stage repair.

We thank Dr. David Minninberg for guidance in establishing this technique.

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For prescribing information see page 202

Presidential Address, 1988. Surgical Research: Its Importance in the Evolution of the Specialty of General Surgery

Bernard Langer, MD, FRCSC, FACS

General surgery is a specialty that has gradually been defined by the evolution of surgery in general, the major events being the identification and separation of subspecialties. Advances in knowledge brought about by research have been the major determinants in allowing the development of these subspecialties. Research has played a major role in the redefinition of general surgery, which has now in its own right become both the parent specialty and a subspecialty: the parent specialty because of its continued concern with disease states of a general nature, such as trauma, critical care, nutrition, transplantation, oncology; a subspecialty because of its focus on specific areas of surgery, particularly gastrointestinal surgery. Future developments in general surgery depend on fostering research in both the general and specific areas, and also across the whole spectrum from the most basic to applied clinical research.

La chirurgie générale est une spécialité qui s'est définie progressivement avec l'évolution de la chirurgie en général. Les principaux évènements qui ont marqué cette évolution sont l'identification, puis la séparation des sous-spécialités. La recherche est à l'origine de l'avancement des connaissances, déterminant majeur du développement de ces sous-spécialités. La recherche a joué un rôle prépondérant dans la redéfinition de la chirurgie générale, laquelle est devenue, à la fois, la spécialité mère et une sous-spécialité en soi: la spécialité mère, car elle continue de s'intéresser aux états morbides de nature générale tels que traumatismes, réanimation, nutrition, transplantation, oncologie; une sous-spécialité, parce qu'elle s'est concentrée sur des domaines spécifiques de la chirurgie, particulièrement sur la chirurgie gastro-intestinale. Les développements futurs de la chirurgie générale dépendront de l'encouragement accordé à la recherche, aussi bien dans ses aspects généraux que spécifiques, et allant de la recherche la plus fondamentale jusqu'aux essais cliniques d'application.

The Canadian Association of General Surgeons (CAGS) has come a long way in only 11 years. It has concerned itself with a number of important issues. Education has been a top priority and is most apparent in the annual scientific meeting. From the beginning, it was the intention of this organization to appeal equally to the broadly based surgeon in community practice and the highly focused specialist general surgeon in an academic institution. The association has played an important role in establishing new training standards for general surgeons and in recognizing and promoting the development of new and special expertise in general surgery. As you are all aware, this is a constantly changing game, and there has been anxiety about the changes that have taken place in general surgery. When, for example, does specialization become fragmentation, and what will become of the specialty of general surgery as we know it?

In my address today, I would like to review some of the changes that have taken place in the specialty of general surgery, indicating the role of research in bringing about these changes and emphasizing the importance of maintaining strength in research to continue this process of evolution.

Pioneers of Surgical Research

The birth of surgical research occurred in the 18th century, the landmark being the career of John Hunter who "introduced a new spirit of enquiry, a philosophy, which not only transformed the medical theory and practice of his epoch, but profoundly influenced scientific thinking everywhere down to our own times."[1]

A century later, Lord Lister introduced the principles of antisepsis which made possible a remarkable expansion of surgical potential. Surgical research developed in the

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19th century, not only in anatomy laboratories, but especially in the developing field of physiology. The chief figures were Heidenhain in Germany, Eck and Pavlov in Russia and Claude Bernard in France.

In the 20th century there was an explosion of knowledge in all fields of medicine as the scientific method became established and universities developed laboratories dedicated to medical research. Alexis Carrel is a premier example of the new breed of 20th-century surgeon scientist. He carried out some of the earliest experiments using tissue culture of cells. He was interested in organ preservation and developed apparatus for that purpose. His most important work was in the area of vascular surgery where he developed the techniques for anastomosing blood vessels that are still in use today.

W.E. Gallie lived at about the same time as Carrel, and although he is best known for organization of a formal, structured, integrated training program at the University of Toronto, he was also a brilliant, innovative thinker whose research involved the autotransplantation of tissues, particularly fascia in hernia reconstruction and the use of xenograft bone material in the fixation of fractures.

Other notable 20th-century researchers include Frances Moore, a broadly based general surgeon who had no specific organ interest, but worked on the principle of studying the whole patient. Jonathan Rhodes at the University of Pennsylvania and Stanley Dudrick developed a system to provide all of the requirements for maintenance of normal nutrition to patients by the intravenous route. This research expanded the capabilities of surgery and, particularly, those of alimentary tract surgeons.

Lloyd MacLean and his group at McGill University focused on the body's response to injury, particularly immunologic responses. They, along with Altemeier and others in the United States, have emphasized the importance of studying in detail the host response to infection in order to develop better strategies of treating it, especially in the manipulation of nutrition and immunologic factors.

In organ transplantation, no one has contributed as much over as long a time as Tom Starzl. He almost single-handedly created the field of liver transplantation, and carried out fundamental studies of factors involved in liver growth and regeneration which have helped to open up the field of liver surgery in general.

The Surgical Specialties

The development of specific surgical specialties was occurring simultaneously, partly as a result of new capabilities for surgical treatment arising from research and partly from expanding patient care needs. Urology was built around the cystoscope, a unique advance in technology. Thoracic surgery was made possible by the introduction of endotracheal anesthesia and controlled ventilation. In the same way, cardiac surgery did not develop as a unique specialty until the extracorporeal pump oxygenator was perfected. In the course of all this, general surgery has been defined by a process of progressive amputation, the field of general surgery consisting of those parts of the body left behind.

The Changing Face of General Surgery

There have also been major reductions in general surgery as a result of new scientific and technologic advances. In the upper gastrointestinal tract, these include endoscopic procedures such as sclerotherapy for varices, papillotomy for biliary stenosis and stone extraction, coagulation for upper gastrointestinal bleeding and endoscopic removal of polyps in the lower gastrointestinal tract. Lithotripsy has been developed for the nonsurgical management of renal stones and is in its early days of evolution for treating biliary stones.

Pharmacologic developments have also changed the face of surgery. They are best exemplified by the development of H2 blockers and other more advanced drugs which can control gastric acid secretion and have almost eliminated surgery for the elective treatment of duodenal ulcer disease. Chemotherapy for cancer has not had the success anticipated, but has modified our approach to the treatment of some malignant tumours.

Despite these developments, the specialty of general surgery can be kept strong by (a) buying into the scientific and technologic developments rather than worrying about competing with them and (b) taking advantage of the position we hold as the surgical specialty which is concerned about the whole patient.

With regard to technological advances, general surgeons must be involved where these advances are applied to the treatment of surgical diseases. Endoscopy, for example, is an essential part of the alimentary tract surgeon's capability. The CAGS and the general surgical committee of the Royal College of Physicians and Surgeons of Canada have established endoscopy as an essential part of the training of the general surgeon. As endoscopy continues to develop in the future, it is essential that general surgeons be involved in the advances related to it, which also means in the research related to it.

There are other areas where new technology offers alternatives to

surgery. Extracorporeal shock-wave lithotripsy (ESWL) was developed by physicists and engineers under the leadership of a urologic surgeon. In most centres, ESWL for kidney stones has developed as a team approach with the surgeon playing a prominent or leading role and considering this as one of the options in the whole spectrum from long-term medication to open surgical procedures. The applications of this technology to biliary stone disease are currently under study and the same approach must be taken. Extracorporeal shock-wave lithotripsy must develop as complementary therapy to surgery, and stone dissolution and the clinical trials and subsequent treatment protocols must involve general surgeons in leadership roles. This is the rational use of surgical expertise in a disease which is, in its most lethal form, a surgical disease.

Likewise, when other scientific advances are made that may change our own field, we must be sure to develop appropriate expertise. We must understand the pharmacology of new drugs and their applications, and be involved in the cutting edge of science. This is obviously not for every surgeon or surgical investigator, but our surgical research efforts must include appropriate training in this field so that we do research that is current and competitive.

I emphasize that general surgeons must take advantage of their role in the diseases of the whole body. In the area of cancer, new developments in chemotherapy will come from the large pharmaceutical firms. The field of immunotherapy, however, is open and requires an innovative mind and understanding of the fields of immunology and cell biology. It is difficult, but not impossible, for surgeons to compete with pure basic scientists in this area. Clinical research in cancer is the area in which we general surgeons can be most competitive. The ultimate testing of new therapy involves controlled clinical trials, and we are the ones who have the patients to carry out these studies.

Transplantation began as a purely surgical specialty with technical problems being predominant. Once the technical problems were solved, immunologic issues became the major limiting factors, and a variety of medical specialists now play a major role in transplantation programs. New immunosuppressive drugs will be tested by pharmaceutical companies, but immunologic manipulation will be developed by scientists with backgrounds in cell biology and immunology. Surgeons must be among those working in the field. We, as surgeons, still tend to be preoccupied with the technical aspects of the operation and to leave patient selection and preparation, postoperative care and follow-up to others. This is a mistake. Transplantation is an interdisciplinary field which has a common base in science, and surgeons must play a major role in every aspect of transplantation programs. General surgeons are particularly appropriate to this role.

Another area in which surgeons must maintain an important interest is that of critical care. This includes polytrauma, nutrition, sepsis and organ failure. The general surgeon should be the key individual in trauma centre organization, and in actual resuscitation and management of critically ill patients after injury and surgery. We must also contribute to research in critical care from basic studies of cellular events in organ failure to clinical trials of new therapies.

Universities and Surgical Research

Having considered the role of research in shaping the development of general surgery, I would like now to examine what role the universities play in this kind of research, whether there is any role for the surgeon in clinical practice, and what function the CAGS has in general surgical research.

The role of the university is to train undergraduate students and postgraduate specialists. Included in every university's mission is the need to do research. As Malcolm Brown, former president of the Medical Research Council of Canada, has pointed out, the most important role of research is to create new knowledge. There are, however, two other important reasons for research in university hospital settings. First, research focuses attention on the diseases being studied in such a way that there is much closer and more systematic assessment of patient selection, outcome and follow-up; as a result, patient care is better. The other important role of research is in helping to create an environment of critical thinking and questioning, so that students and residents will develop better judgement, literature evaluation skills and appraisal of existing dogma.

Role of the Practising General Surgeon

This brings me to the role of those of you who are surgeons in busy clinical practice. You are obviously not in a position to do research yourselves. It is important, however, to maintain a sense of enquiry and questioning of existing practice. If those of you who are over 50 years old remember how you treated breast cancer during your residency and compare that with the way you treat it now, you will recognize how important it is to be aware of change and the need for a good set of standards to evaluate

what appears in the literature as an advance in knowledge. Do you remember the excitement about gastric freezing and how large numbers of freezing machines were sold, not to mention the thousands of patients who had their stomachs frozen, before it finally became apparent that not only did this new treatment not work, but there were serious complications as a result of it?

Surgical Research and CAGS

The role of the CAGS in research development is to support and promote research in general surgery in every way possible. This was recognized at the time our organization was founded. In addition to our advisory committee on research, and under the leadership of Neil Watters, we have created the Canadian Surgical Research Fund to promote, lobby and raise money for general surgical research — for specific projects, for residents-in-training and to support research training fellowships. Three potential sources of funds include patients, industry and our membership, which is the major source of income. The contributions of our members attest in a tangible way to their commitment to supporting research. Much more is needed and the members of the Board of the research fund are seeking ways to tap other sources. Our patients have shown their willingness to support research — but they have to be asked. You, our members, can help by approaching your patients to support the Canadian Surgical Research Fund. You will be pleasantly surprised at the response.

The General Surgeon's Support for Surgical Research

The final question is, How are we doing overall in relation to research in general surgery? In a nutshell, we are not doing as well as we should. Interest in research has increased in medical schools in terms of numbers of summer students and research fellows, but major problems exist.

Funding for research in general has decreased in terms of real dollars, particularly in the area of surgical research. This has occurred both in the US and Canada, because of the increasing sophistication of basic research and the difficulty clinicians, especially surgeons, have in competing with full-time basic scientists for limited research dollars. We have responded by increasing the training period for committed surgeon/scientists and moving to develop within surgical departments groups of investigators that include dedicated basic scientists.

Another problem is the peer-review system in granting agencies on whose committees, for a variety of reasons, surgeons are often not represented. The Canadian surgical chairmen have formed the Canadian Council on Surgical Research to act as a lobby group and, it is hoped, help to secure increased representation of surgeons in the review process of scientific granting organizations.

Another problem has been the difficulty of maintaining the career path of the surgeon/scientist in a clinical department. This involves a complexity of issues including time protection, financial support and image, all of which are now being addressed.

Regarding the general surgical community at large, there is a need for support in terms of such bodies as the Canadian Surgical Research Fund. The CAGS has responded to that need. Those dollars, however, will always be a relatively small part of the overall support required. Of equal importance is the role of surgeons in the community and of the regional surgical societies in recognizing the value of research, in transmitting the knowledge gained to their patients, and where possible in helping to convince politicians and other legislators of the need for increased research support.

Future of General Surgery

What does the future hold for general surgery? Perhaps the best way to answer this is to look through the window provided by those currently working at the cutting edge in our medical schools. A conference supported by the Canadian Surgical Research Fund was held in Mississauga last June. The topics covered by these young researchers included the following.

- "Regulation of intracellular pH in resident and activated peritoneal macrophages". In this study the researchers are trying to identify the molecular mechanisms that lead to activation of peritoneal macrophages. It is a very important issue in our host defences in peritonitis and of interest to every abdominal surgeon.
- "31P NMR spectroscopy of liver and skeletal muscle in a model of cancer cachexia". New technology of surface coil spectroscopy is being used to measure serially visceral energy stores in an experimental model of cancer cachexia. This may provide a simple way to assess nutritional deficits in cancer patients.
- "Allotransplantation of single donor purified canine islets into the spleen or renal subcapsular space using cyclosporine". This very exciting piece of work won the CAGS Resident's Research Prize for 1988. It is a study of transplantation of highly purified islets in diabetic dogs. Many investigators believe that islet transplantation is more likely to be successful in managing

the difficult human diabetic than whole organ transplantation.

- "Islet cell differentiation and proliferation induced by pancreatic cytosol extract". This important investigation was carried out in hamsters to study the factors that promote growth and development of islets. Such factors will be essential in developing the ultimate techniques for islet transplantation in the human.
- "Extracorporeal shock-wave lithotripsy (ESWL): a valuable adjunct in the management of difficult biliary tract calculi". This is a preliminary report of clinical experience. It is the equivalent of a phase II cancer trial and is very important at present; ultimately, carefully controlled prospective studies will be required.
- "The reversal of cyclosporine: a mediated suppression of allogeneic induced monocyte procoagulant activity by H2 antagonists in vitro". Most transplant patients must take multiple drugs. This study documents the potentially detrimental effect that H2 blockers may have on cyclosporine immunosuppression in transplant patients.
- "The critical injury of cold preservation of liver allografts in the rat is sinusoidal lining cell damage". This is a careful morphologic study in the rat, demonstrating the typical endothelial cell injury characteristic of cold preservation of the liver during transplantation. This provides a simple model for the study of better preservation techniques and focuses attention on an important target cell in preservation injury.
- "The effect of cisplatin on liver regeneration in the rat after two-thirds hepatectomy". The results of this experimental study of chemotherapy on liver regeneration will have a bearing on the role of adjuvant chemotherapy in patients after resection of hepatic tumours.

These are some of the studies which will change the way in which we practise and will redefine the specialty of general surgery. We have come a long way since I became a general surgeon 25 years ago. I expect we will progress even further in the next 25. I hope that I will be around to see it and I know that many of you, and certainly the Canadian Association of General Surgeons, by which I have been honoured as president, will play an important role in continuing to shape the specialty of general surgery. ■

SESAP VI Question

Item 105

The most frequently encountered metabolic complication of urinary diversion through an ileal segment is

(A) hyperkalemic, hypochloremic metabolic acidosis

(B) hyperchloremic metabolic acidosis

(C) hypokalemic metabolic alkalosis

(D) hypochloremic metabolic alkalosis

(E) combined metabolic acidosis and respiratory alkalosis

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

For the critique of Item 105 see page 170.

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Corrections

In the January 1989 issue, the article entitled "Acute scrotal pain in children: prospective study of diagnosis and management", which appears on pages 29 to 32, contains an error. On page 31 the illustrations for Figs. 1 and 2 are reversed, but the legends are correct. The left-hand picture illustrates a case of spermatic cord torsion and the right-hand figure a case of epididymitis. We apologize to both the authors and our readers for this mistake.

Also in the January 1989 issue, the name of R.M. Baird, MD, FACS, FRCSC, was inadvertently omitted as one of the coauthors of the article "The risk of occult invasive breast cancer after excisional biopsy showing in-situ ductal carcinoma of comedo pattern", which appears on pages 56 to 60.

Carotid Body Tumours: the University of Alberta Hospital Experience

F.A. Daudi, MD; O.G. Thurston, MD, FRCSC

At the University of Alberta Hospital between 1950 and 1988, 17 patients who had a diagnosis of carotid body tumour were seen; 15 of them were followed up for an average of 8 years (range from 1 to 38 years).

In 14 patients the tumour was removed surgically. There were no operative deaths and no strokes occurred. The most frequent complication was cranial nerve deficit. Of the 15 patients followed up, 10 (67%) manifested a deficit of the facial, vagus or hypoglossal nerve.

The primary tumour was diagnosed histologically as a benign neoplasm in all 14 patients operated on, but in 3 distant metastases developed or there was invasive local recurrence. Patients with malignant tumour were significantly ($p \leq 0.01$) younger than those with a benign tumour.

Carotid body tumours can be managed safely with respect to stroke complications, but cranial nerve injuries continue to be a problem. Malignant tumours are difficult to distinguish from benign tumours except that they tend to occur in younger patients. Prompt surgery and close follow-up is particularly important in patients with carotid body tumour.

Entre 1950 et 1988, 17 patients de l'hôpital de l'Université d'Alberta ont reçu un diagnostic de tumeur du glomus carotidien; 15 d'entre eux ont été suivis pendant une période moyenne de 8 ans (écart de 1 à 38 ans).

Chez 14 patients, la tumeur fut enlevée chirurgicalement. Il n'y eut pas de mortalité peropératoire et aucun accident cérébrovasculaire n'est survenu. La complication la plus fréquente fut un déficit des nerfs crâniens. Des 13 patients qui ont survécu et qui ont fait l'objet d'un suivi, 10 (77%) manifestaient un déficit des nerfs facial, vague ou hypoglosse.

La tumeur primitive fut diagnostiquée histologiquement comme tumeur bénigne chez chacun des 14 patients opérés bien que, dans 3 cas, il y eut métastase à distance ou récidive avec envahissement local. Les patients porteurs de tumeurs malignes étaient significativement plus jeunes ($p < 0.01$) que ceux qui souffraient de tumeurs bénignes.

Les tumeurs du glomus carotidien peuvent être traitées sans crainte d'un accident cérébrovasculaire, mais les lésions des nerfs crâniens sont une complication courante. Les tumeurs malignes se distinguent difficilement des tumeurs bénignes, sauf qu'elles semblent survenir chez des patients plus jeunes. Une chirurgie précoce et une surveillance étroite des suites thérapeutiques sont particulièrement importantes chez les patients souffrant d'une tumeur du glomus carotidien.

From the Department of Surgery, University of Alberta, Edmonton, Alta.

Presented at the 11th annual meeting of the Canadian Association of General Surgeons, held in conjunction with the 57th annual meeting of the Royal College of Physicians and Surgeons of Canada, Ottawa, Ont., Sept. 24, 1988

Accepted for publication Oct. 13, 1988

Reprint requests to: Dr. O.G. Thurston, Department of Surgery, 2D4.36 Mackenzie Health Sciences Centre, The University of Alberta, Edmonton, Alta. T6B 2B7

Carotid body tumour is an uncommon neoplasm which arises from paraganglionic cells at the bifurcation of the common carotid artery. The tumour is extremely vascular. However, in the follow-up of patients operated on for carotid body tumours we have noted that cranial nerve complications have been more numerous and more seriously disabling than vascular complications. We believe that because surgeons are preoccupied with potential vascular complications, vascular control is well handled, but neurologic complications, because of cranial nerve damage, remain a challenge. In this study of 17 patients with carotid body tumours we have attempted to demonstrate the importance of cranial nerve complications.

Patients and Methods

Between 1950 and 1988, 17 patients seen at the University of Alberta Hospital in Edmonton had a diagnosis of carotid body tumour. The medical records of these patients were reviewed and data tabulated with particular attention to duration of symptoms, methods of investigation, operative findings and techniques, postoperative complications and histologic features of the tumours. Fifteen patients were followed up by clinic visit or letters from other physicians with particular attention paid to persisting disabilities and tumour recurrence.

Findings

The 17 patients (7 men and 10 women) ranged in age from 15 to 79 years (mean 48 years). All presented with a neck mass which had been present from 2 months to 13 years. Three patients had bilateral tumours and three had a family history of carotid body tumour. Diagnosis was confirmed by arteriography in 12 patients; computed tomography was also done in 2 of these. In four patients the diagnosis was made at the time of neck exploration and in one patient by computed tomography alone, carried out just before surgery. Fourteen patients underwent surgical resection of the tumour. In 13 of these, an adventitial dissection and resection was carried out after securing proximal and distal vascular control. In one patient, the carotid bifurcation was resected and common-to-internal carotid artery continuity was restored with a saphenous vein graft. Three patients were not operated because of advanced malignant disease not related to the carotid body tumour, previous stroke and pending resection of an adrenal pheochromocytoma. Immediate postoperative complications were hematoma requiring reexploration of the neck in two patients. There were no operative deaths. Pathological examination of excised tumours confirmed the diagnosis of benign carotid body tumour in all 14 patients.

The mean follow-up of the 15 patients was 8 years (range from 1 to 38 years). At the time of writing, eight patients were alive and free of recurrent tumour. Four patients died of unrelated causes. One patient died of metastatic carotid body tumour in bone. One patient was alive with metastatic carotid body tumour to the spine and associated paraplegia. One patient was alive with locally recurrent carotid body tumour extending to the base of the skull. Thus, in 3 of the 15 patients the tumour behaved in a malignant fashion, although this was not anticipated from the histologic appearance of the primary tumour. The age of these 3 patients was 25 ± 9 years (mean ± SD) whereas the age of the 14 other patients was 53 ± 15 years ($p \leq 0.01$, Student's *t*-test).

The 15 patients available for follow-up showed a high incidence of persisting cranial nerve deficits. Voice changes, including hoarseness and inability to raise the voice to a loud level, were noted in six patients. Three patients had a unilateral (and ipsilateral) hypoglossal nerve palsy and one patient had a palsy of the marginal mandibular branch of the facial nerve. Thus, 10 of 15 patients (67%) had a localized deficit of the facial, vagus or hypoglossal nerve.

Discussion

In this series, postoperative vascular complications were confined to two postoperative hematomas, which required evacuation. No patient suffered a stroke either intraoperatively or postoperatively, and there were no operative deaths. However, postoperative complications related to cranial nerve lesions were noted frequently, and this has been a consistent finding in series of patients with carotid body tumours reported from other institutions.[1-3] Surgeons operating on patients with carotid body tumours have become increasingly aware of the devastating effects of interruption of carotid blood flow. As a result, the perioperative mortality and stroke rates have fallen dramatically in the last 20 years[4] as vascular techniques have been refined.

Unfortunately, the rate of cranial nerve injuries has not fallen correspondingly. Low death and stroke rates for carotid body tumour resection should result in patients being operated on sooner for carotid body tumours when they are relatively small (stage I in the classification of Shamblin and colleagues[5]). Small tumours, an awareness of potential cranial nerve injury and refinement of technique[6] should result in a decline in the incidence of cranial nerve injuries resulting from the removal of carotid body tumours.

There is general agreement that it is difficult to predict the malignant potential of carotid body tumours from the histologic appearance of the primary tumour, although cellular pleomorphism has been observed to be an indication of malignancy.[2] In our series, one patient had local recurrence of the primary tumour after what was considered to be a complete excision and two patients had frank metastases to bone. In each case, the primary tumour was thought to be benign pathologically. This is in keeping with the findings of Meyer and colleagues[6] who noted a metastatic rate of about 5% for carotid body tumours regardless of histologic appearance. In this series of patients, young age at the time of diagnosis was a more reliable index of aggressive tumour behaviour than the histologic appearance of the tumour. This finding argues for early surgery and close follow-up for patients in the second, third and fourth decades of life, who have a carotid body tumour.

The majority of patients with carotid body tumours present with a unilateral lesion and have no family history of this condition. However, familial occurrence and bilateral lesions have been documented. Bleker and Wereldsma[7] noted a 25% incidence of bilateral tumours in patients with a family history compared with 5% otherwise. Three patients in our series

had a family history and one of them had bilateral tumours. The other patient with bilateral carotid body tumours had no family history. The patient with bilateral carotid body tumours and a positive family history of the tumour was also found to have an adrenal pheochromocytoma. This association has been noted[8] and represents an additional consideration in the work-up preoperatively of patients with carotid body tumours.

Carotid body angiography has been the gold standard for the diagnosis of carotid body tumours, its accuracy approaching 100%.[3] Computed tomography shows a well-circumscribed, strong contrast enhancing mass at the bifurcation of the common carotid artery and these findings appear to be typical of this lesion.[9] In one of our most recent patients, the combination of clinical assessment and computed tomography accurately defined the lesion, and this patient was operated on without difficulty. We believe that as more experience is gained with computed tomography, it will replace angiography in the diagnosis of carotid body tumours, except in special situations in which carotid body stenosis is suspected or in the rare situation when embolization is contemplated before surgery.

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NOTICES

Annual Meeting of American Society of Colon and Rectal Surgeons

More than 1000 surgeons are expected to attend the 88th annual meeting of the American Society of Colon and Rectal Surgeons which will be held in Toronto, June 11–16, 1989. The program features workshops, guest lectures, exhibits and, of particular interest, a panel discussion on the optimal surgical technique for colorectal cancer. For further information contact: Executive Office, The American Society of Colon and Rectal Surgeons, Ste. 1080, 800 East Northwest Highway, Palatine, IL, 60067, USA; (312) 359-9184.

Continuing Education at University of Toronto

A course entitled "Hepatic Surgery: New Anatomy, New Techniques" is being offered by the Faculty of Medicine at the University of Toronto. Further information about the course, which is scheduled for Sept. 18, 1989, can be obtained from the Department of Continuing Education, Faculty of Medicine, University of Toronto, Medical Sciences Building, Toronto, Ont. M5S 1A8; (416) 978-2718.

Urologic Oncology

Toronto will also be the setting for a conference Oct. 12–14, 1989 entitled "Urologic Oncology: Today & Tomorrow". Dr. John Trachtenberg of Toronto is the conference chairman. More information can be obtained from Jeanie McGoldrick, Conference Coordinator, Stratagem Communications, Ste. 604, 2 Sheppard Ave. E, Willowdale, Ont. M2N 5Y7; telephone (416) 229-2331; fax (416) 229-6443.

Royal College Annual Meeting

The 58th annual meeting of the Royal College of Physicians and Surgeons of Canada will be held Sept. 22–25 in Edmonton. The program includes postgraduate courses, poster sessions, workshops, symposia, free communication sessions and medical and surgical exhibits. Over 2500 specialists, interns and residents are expected to attend. For further information contact Anna Lee Chabot, Head - Meetings and Assemblies Section, Office of Fellowship Affairs, The Royal College of Physicians and Surgeons of Canada, 74 Stanley Ave., Ottawa, Ont. K1M 1P4; (613) 746-8177.

CMA Annual Meeting

The Canadian Medical Association's 122nd annual meeting is scheduled for Aug. 20–25, 1989 in Quebec City. In conjunction with the meeting, a scientific program on "highway traumatology" is being offered by the CMA and the "Régie de l'assurance automobile du Québec". Further information can be obtained from the CMA Meetings Department, PO Box 8650, Ottawa, Ont. K1G 0G8; (613) 731-9331.

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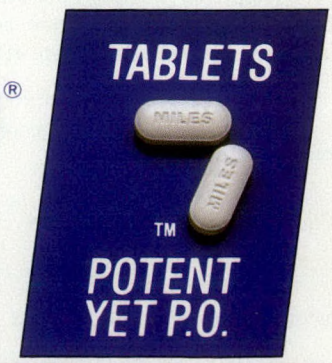

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Surgical Treatment of Peritoneal Carcinomatosis: 1988 Du Pont Lecture

Paul H. Sugarbaker, MD, FACS*

Tumour spread onto peritoneal surfaces is frequent in patients who have recurrent gastrointestinal cancer. In this study the author describes (a) a cytoreductive surgical technique of ball-tipped electrocautery dissection, which can rapidly and definitively remove large volumes of intra-abdominal tumour, (b) a procedure for immediate postoperative lavage of the abdominal cavity to remove blood and tissue debris, and (c) a regimen of early and delayed intraperitoneal chemotherapy to destroy small quantities of residual cancer cells on intra-abdominal surfaces. Forty-seven patients underwent cytoreductive surgery to remove large volumes of adenocarcinoma widely disseminated through the abdomen. Most patients had intraperitoneal chemotherapy to destroy small volumes of cancer remaining within the abdomen. In the absence of previous radiotherapy, one patient died and the morbidity was acceptable. In eight patients who received radiotherapy, seven had bowel perforation and one died. Surprisingly, the majority of patients who had cytoreductive surgery plus intraperitoneal chemotherapy had disease-free long-term survival. In patients with peritoneal carcinomatosis, long-term disease-free survival correlated with low tumour aggressiveness, adequate cytoreductive surgery and the use of intraperitoneal chemotherapy.

Chez les patients souffrant de cancer gastro-intestinal, l'envahissement tumoral des surfaces péritonéales est fréquent. L'auteur décrit a) une technique de dissection à l'électrocautère à pointe mousse permettant de réduire rapidement et définitivement de telles tumeurs, b) une technique de lavage postopératoire immédiat de la cavité abdominale pour éliminer le sang et les débris tissulaires, et c) un régime thérapeutique composé d'une chimiothérapie intrapéritonéale immédiate et retardée, destinée à éliminer de petites quantités de cellules cancéreuses résiduelles sur les surfaces intra-abdominales. Quarante-sept patients ont subi une chirurgie cytoréductrice d'importantes masses d'adénocarcinomes largement disséminés dans l'abdomen. La plupart des patients reçurent une chimiothérapie pour détruire de petites masses tumorales qui restaient dans l'abdomen. En l'absence de radiothérapie préalable, un patient est décédé et la morbidité fut acceptable. Des huit patients qui reçurent de la radiothérapie, sept subirent une perforation intestinale et un mourut. On a constaté avec étonnement que la majorité des patients qui eurent une chirurgie cytoréductrice accompagnée d'une chimiothérapie intrapéritonéale, a bénéficié d'une survie à long terme, exempte de rechute. Dans les cas de carcinomatose péritonéale, une survie libre de maladie, de longue durée, correspond à une tumeur peu agressive, à une chirurgie cytoréductive adéquate et à une chimiothérapie intrapéritonéale.

From the Department of Surgery, Emory University School of Medicine, Winship Clinic and Cancer Center, Atlanta, Ga.

Presented as the Du Pont Lecture at the annual meeting of the Southern Ontario Surgical Society, Stratford, Ont., June 3, 1988

**Sponsored as visiting professor by Du Pont Canada Inc., Mississauga, Ont.*

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Reprint requests to: Dr. Paul H. Sugarbaker, Winship Cancer Center, 1327 Clifton Rd. NE, Atlanta, GA 30322, USA

The surgical treatment of cancer is dictated by the anatomic location of the tumour and its histologic grade of malignancy. In lesions of low-grade malignancy, such as mucinous adenocarcinoma which may appear in the colon or appendix, resection including minimal margins (less than 1 mm) of healthy tissue has resulted in cure. Unfortunately, when this tumour extends through the bowel wall, mucin-producing cells disseminate throughout the peritoneal cavity. The resulting clinical entity is commonly referred to as cystadenocarcinoma, malignant pseudomyxoma peritonei or mucinous peritoneal carcinomatosis. In the past, it was considered impossible to render patients who had peritoneal carcinomatosis clinically free of tumour.

I shall describe a technique for cytoreductive surgery and intraperitoneal chemotherapy and report the results to date in a group of patients who had these treatments for peritoneal carcinomatosis from colonic and appendiceal cancer.

Surgical Problems Posed by Peritoneal Carcinomatosis

Peritoneal carcinomatosis is characterized by an "omental cake" of tumour attached to stomach and colon (Fig. 1). It can usually be removed by a combined omentectomy-splenectomy; however, if the colon is encased by tumour, an en-bloc resection of omentum, spleen and abdominal colon may be necessary. Next to stomach and

colon, the pelvic peritoneum is most frequently affected; the cul-de-sac is generally filled by tumour. Also involved are the undersurfaces of the right and left hemidiaphragm, the right suprahepatic space between the diaphragm and liver and the inferior aspect of the liver (right subhepatic space) just above the right kidney. Tumour beneath the right hemidiaphragm may fix liver and diaphragm together. The right and left paracolic gutters may be filled by tumour adherent to peritoneum. The fatty tissue of the porta hepatis, falciform ligament and lesser omentum are often involved; the gallbladder and porta hepatis are commonly a single mass of cancer.

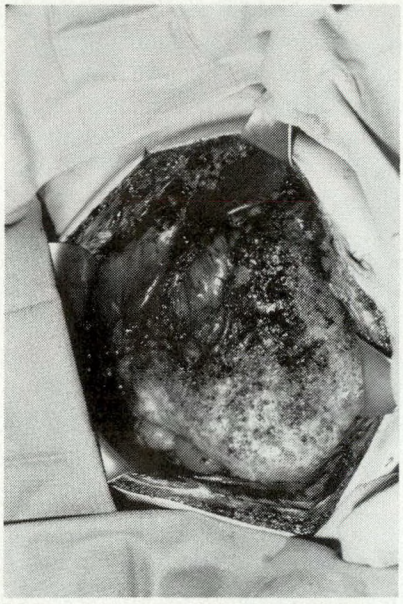

FIG. 1. "Omental cake" is characteristic of peritoneal carcinomatosis. It involves omentum, spleen and may encase abdominal colon.

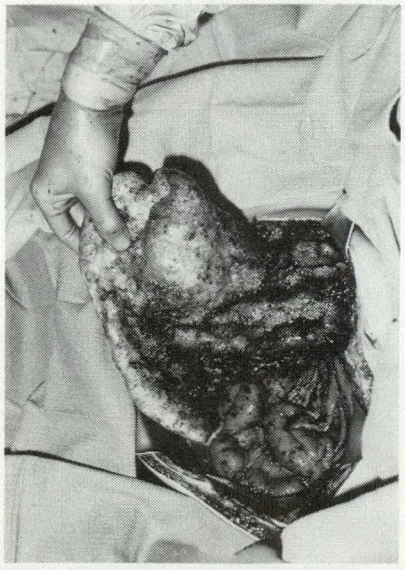

FIG. 2. Small-bowel sparing by peritoneal implants. Even though thick layers of tumour are present on most abdominal surfaces, small-bowel surface is relatively spared of tumour. Portions of small bowel fixed to abdominal wall are at ligament of Treitz and terminal ileum. These sites may be encased in mucinous tumour.

One aspect of this condition, not previously appreciated, is the relative sparing of small-bowel surfaces by tumour implants (Fig. 2), believed to be due to peristalsis. Only after several laparotomies will the small bowel become encased by tumour, because tumour emboli adhere to abraded peritoneum and are trapped within fibrous adhesions on small-bowel surfaces. Continued growth of tumour within small-bowel adhesions makes cytoreduction unsafe.[1] However, early in the disease, removal of tumour from peritoneal surfaces can be accomplished without trauma to the small bowel. There are two exceptions to this tumour-sparing effect. The terminal ileum and ligament of Treitz are both anchored to the retroperitoneum. These anatomic sites are much less mobile than the remaining small bowel and may be encased by tumour. The terminal ileum must often be resected with the cecum. Wedge excision of small bowel at the ligament of Treitz may also be necessary.

The optimal timing for the cytoreductive procedure may not be the same in all patients. Ideally, removal of bulky tumour, including greater omentum, and opening up of all abdominal adhesions should be accomplished before intraperitoneal chemotherapy is started. Some patients will be referred for definitive treatment of peritoneal carcinomatosis shortly after exploratory laparotomy. They are often not capable, physically or emotionally, of enduring a major abdominal procedure at that time. Placement of a peritoneal access device and several cycles of intraperitoneal chemotherapy are used to preserve gastrointestinal function and reduce small-volume disease on peritoneal surfaces. If the disease does not disseminate to distant sites and the patient's physical status improves over 4 to 6 months, then definitive treatment of peritoneal carcinomatosis with cytoreductive surgery is indicated.

Surgical Technique for Cytoreduction

With sufficient courage, knowledge of anatomy, patience and persistence, the surgeon can dissect all peritoneal surfaces within the abdomen free of tumour using ball-tipped electrocautery on pure cut and at high voltage (Table I). Dissection with the ball tip just beneath the tumour leaves visceral structures intact, removing only the lesion and involved peritoneal surfaces. An important aspect of this technique is strong traction and countertraction between tumour and normal tissue (Figs. 3 to 5). This will expose vascular and ductal structures and avoid damage to them as the dissection proceeds. Electrocautery on pure cut evaporates tumour tissue and does little damage to fibrous tissue and normal fat, so normal anatomic structures encased in fat but covered by mucinous tumour should not be affected. Tissues rich in collagen, such as ureters, large blood vessels, common duct and intestinal wall may be severely damaged unless the surgeon's technique is meticulous and these structures are irrigated

frequently with cool water during the procedure.

The undersurface of the diaphragm poses special problems. If the ball-tipped electrocautery contacts diaphragmatic muscle, marked unpredictable contractions occur; the cautery tip may perforate the hemidiaphragm or pericardium. Tumour in this area is best removed using a combination of blunt dissection and contact yttrium-aluminum-garnet (YAG) laser. The latter will maintain hemostasis and a margin of dissection but will not cause contractions of diaphragmatic muscle. An essential piece of equipment for this procedure is the laser smoke evacuator, which minimizes the foul odour and excessive smoke, thus maintaining the surgeon's view of the operative field, and eliminates the possible inhalation hazard to operating-room personnel.

In patients who must undergo reoperation, tumour within fibrous adhesions must be removed from small-bowel surfaces, and this can be hazardous. Frequent irrigation of the operative site with saline will minimize the possibility of full-thickness thermal damage to bowel wall. If multiple areas of the bowel are damaged, then a high, diverting loop jejunostomy should be brought out through a transverse incision in the left upper quadrant. This will prevent the formation of small-bowel fistulas and associated intraperitoneal sepsis. When pelvic tumour implants are removed there may be trauma to the large bowel, requiring temporary exteriorization of the sigmoid colon. The ostomies are closed when bowel integrity is demonstrated radiologically.

Cytoreduction of tumour in the porta hepatis presents a special problem. Cystadenocarcinoma characteristically implants and grows in the "nooks and crannies" of the abdomen. The recesses created by the gallbladder, falciform ligament and common-duct structures are usually heavily involved by tumour. An ultrasonic dissector has been a valuable tool by which to remove the mucinous cancer (high in water content) from around the vital tubular structures (high in collagen content) that constitute the porta hepatis.[2]

Gross tumour within the lesser omentum may require a lesser omentectomy with sacrifice of the right branch of the vagus nerve and a portion of the left gastric artery. If this is needed, a gastric drainage procedure (pyloroplasty or gastrojejunostomy) should be performed.

Technique for Immediate Postoperative Intraperitoneal Lavage

When the dissection is completed, a Tenckhoff catheter is placed through the abdominal wall at a convenient location lateral to the rectus muscles and anchored at the peritoneal level by a pursestring suture.

Postoperatively, the abdominal cavity is lavaged for 24 hours with a dialysis solution containing antibiotics. This will remove blood and tissue debris, which may plug the catheter, and will help prevent infection and the formation of adhesions (Table II).

Table I. Requirements for Dissection of Gastrointestinal Tumour From Peritoneal Surfaces

1. Meticulous bowel preparation, removing bacteria and fungus from the gastrointestinal tract.
2. Electrocautery machine placed on high voltage, pure cut, with the ball tip employed for tissue contact.
3. Strong traction-counter traction placed at the tumour–healthy tissue interface.
4. Use of laser smoke evacuator.
5. Frequent irrigation for cooling nearby tissues when the dissection is used adjacent to a vital structure such as small bowel, ureter or common duct.
6. Wide exposure using a self-retaining retractor.
7. Postoperative peritoneal lavage to remove tissue debris. Large-volume instillations in the immediate postoperative period should contain antibiotics.
8. Intraperitoneal chemotherapy to minimize the recurrence of microscopic residual disease. Lavage fluid should contain antibiotic agents.

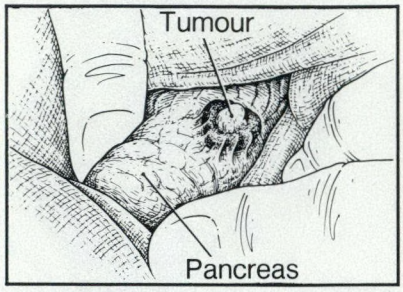

FIG. 3. Mucinous tumour implant on peritoneal surface overlying pancreas.

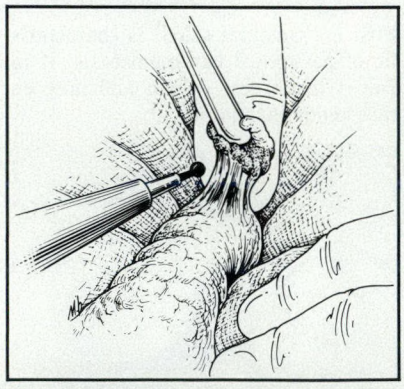

FIG. 4. Traction at tumour–normal tissue interface. Ball-tipped electrocautery on pure cut at high voltage is used to evaporate tumour and separate it from normal tissue.

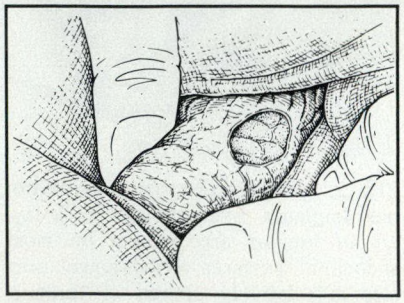

FIG. 5. Tumour-free abdominal surface following electrocautery dissection. Damage to underlying pancreatic tissue is minimal.

To minimize catheter-related complications, there must be meticulous hemostasis, and the peritoneal cavity must be irrigated clear of blood and clots before the abdomen is closed. Cytotoxic agents used for intraperitoneal chemotherapy prevent neutrophil replication within the abdominal cavity for the first week postoperatively, so antibiotics are needed in the lavage solution to control bacterial growth.

Drains in the abdomen should be of the closed suction type, placed low in either flank so that they can be used for dependent drainage if peritonitis occurs (Fig. 6). When early postoperative intraperitoneal chemotherapy is completed and intraperitoneal drainage ceases, the Romel tourniquets, used to provide a watertight seal, are removed. This allows gravity drainage of any recurring intra-abdominal fluid, which will help to prevent late abscess formation. It also facilitates removal of the suction drains, which are usually placed beneath the left hemidiaphragm and occasionally within the pelvis.

Peritoneal lavage can be performed postoperatively in patients who have ostomies, but leakage of intraperitoneal fluid will be excessive unless the bowel wall is secured circumferentially with individual sutures to the peritoneum plus fascia.[3]

Intraperitoneal Chemotherapy

Cytoreductive surgery to remove malignant tumour usually results in limited short-term benefit to patients. Bowel obstruction can be relieved and bulk tumour removed. Yet long-term disease-free survival cannot be achieved unless the extensive tumour contamination of intra-abdominal surfaces can be controlled. The use of early and delayed postoperative intraperitoneal chemotherapy has been used successfully to eliminate from the abdominal cavity single cancer cells and tumour emboli. These malignant foci become imbedded in the fibrinous exudate that accumulates on raw tissue surfaces within the abdomen after surgical trauma.[4] They develop into recurrent peritoneal carcinomatosis over time no matter how complete the surgical cytoreduction.

Intraperitoneal chemotherapy has been used to combat the regrowth of cancer within the fibrous adhesions that form after cancer surgery. Optimally, the drugs should be instilled in a large volume of fluid to distend the abdomen and reach all exposed surfaces. The chemotherapy does not penetrate tumour masses of appreciable size but should destroy all small-volume disease. It is best utilized in the first 5 postoperative days when drug distribution to all intra-abdominal surfaces is complete. Delayed postoperative intraperitoneal chemotherapy is designed to augment the effects of the surgery and the early postoperative intraperitoneal chemotherapy. Drug distribution is less uniform after abdominal adhesions have formed and retroperitoneal fibrous reaction has occurred. The current plan for early and late intraperitoneal chemotherapy for large bowel tumours is shown in Table III.

Table II. Abdominal Lavage Instilled Immediately After Completion of Surgery

1. Instill 1 litre 1.5% dextrose peritoneal dialysis fluid as rapidly as possible. The fluid should contain antibiotics for broad-spectrum coverage.
2. One hour dwell time, drain fluid as rapidly as possible.
3. Repeat instillations every 1 hour four times, then every 4 hours four times, then every 8 hours until chemotherapy begins.

Patient Groups

Forty-seven consecutive patients with advanced primary or recurrent colorectal or appendiceal tumours underwent laparotomy and cytoreductive surgery; none were merely explored surgically, the abdomen closed and no further action contemplated. They ranged in age from 16 to 74 years. They were divided into four groups. Group 1 (18 patients) represented the ideal situation in which patients had grade 1 or less mucinous cancer. All had malignant pseudomyxoma peritonei; no patient had benign mucocele of the appendix.[1] Group 2 patients (17) had moderate- to high-grade mucinous colonic or rectal adenocarcinoma implanted on peritoneal surfaces, but had no hematogenous or distant lymphatic metastases. Group 3 patients (eight) had either high- or low-grade tumour that had been treated with radiation (abdominal or pelvic) or intraperitoneal iodine-131 monoclonal antibody. Group 4 (four) had peritoneal carcinomatosis and, subsequently, distant metastases.

In each group of patients, some were treated with intraperitoneal chemotherapy and some were not. In patients who did not receive intraperitoneal chemotherapy, abdominal infection or an adhesive process developed that prevented

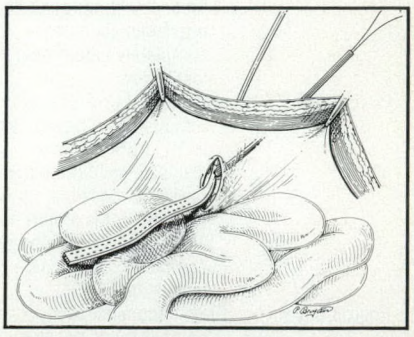

FIG. 6. Romel tourniquet used to provide watertight seal around closed suction drains inserted through generous stab incisions.

drug delivery by a peritoneal access device.

Results

All of the low-grade mucinous tumours were of appendiceal origin. Moderately differentiated but clinically nonmetastasizing tumours originated in the appendix (six) and other parts of the colon (eleven). Nearly all of the 47 patients were symptomatic before they were treated for peritoneal carcinomatosis. The asymptomatic patients had lethal seeding of peritoneal surfaces, established by a previous laparotomy and a rising carcinoembryonic antigen level.

The short-term results of the ball-tipped electrocautery technique were surprisingly good. All patients but one had at least transient relief of intestinal obstruction. Patients who seemed to profit most over the long term had three clinical features in common (Table IV). First, and most important, they did not have distant lymphatic or hematogenous spread of the disease. Of four patients with metastases (group 4), only one remains disease free, and he underwent a pneumonectomy for lung metastases. Second, patients who were made clinically disease free by cytoreductive surgery seemed to be in a favourable group, even though some required several staged surgical procedures to reach this status. Of course, a larger proportion of low-grade cancers were completely removed. Finally, only patients who had intraperitoneal chemotherapy or immunotherapy, in addition to surgery, remained well for long periods. Over half of the patients with mucinous adenocarcinoma may be expected to have prolonged disease-free survival. They represent the first report of cure after treatment for peritoneal carcinomatosis.

Unfortunately, in these early clinical studies, these favourable results were not obtained without cost. The majority of patients who had cytoreductive surgery after abdominal radiotherapy had bowel perforation postoperatively. A similar complication occurred in four of the patients who did not have preoperative abdominal radiotherapy. There were no cases of anastomotic breakdown. Of the patients who did not have radiotherapy preoperatively, six had peritonitis in the presence of an intact bowel. The organisms were *Staphylococcus epidermidis* and *Candida albicans*. There were two postoperative deaths, one from staphylococcal pneumonia and the other from the formation of multiple fistulas in a patient who had irradiated bowel.

Discussion

Complications of cytoreductive surgery are frequent, the most severe being seen in patients who have previously undergone abdominal or pelvic radiotherapy. I recommend that such patients be excluded from this treatment plan unless all of the irradiated tissue can be resected.

If this procedure is attempted in the presence of invasive tumours, there may be dangerous hemorrh-

Table III. Early and Delayed Postoperative Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis from Large-Bowel Cancer

Time	Cycle 1	2*	3*	4*
Day of surgery	Abdominal lavage only			
Postop day 1	Mit C 10 mg/m^2 in 1 L 1.5% dextrose dialysate solution. Infuse as rapidly as possible; 23-hour dwell time. Maximum dose 20 mg. Drain abdomen completely before next instillation	5-FU 900 mg/m^2 plus 50 mmol sodium bicarbonate in 2 L 1.5% dextrose dialysate solution. Infuse as rapidly as possible; 24-hour dwell time and no drainage	Mit C 12 mg/m^2 in 2 L	5-FU 900 mg/m^2 plus 50 mmol sodium bicarbonate in 2 L
Postop day 2 to 5	5-FU 800 mg/m^2 plus 50 mmol sodium bicarbonate in 1 L 1.5% dextrose dialysate solution. Infuse as rapidly as possible; 23-hour dwell time. Maximum dose 1600 mg. Drain abdomen completely before next instillation	Same dose of 5-FU in 1 L solution. The soft tube used for peritoneal access is removed after instillation on day 5	5-FU 900 mg/m^2 plus 50 mmol sodium bicarbonate in 1 L	Same dose of 5-FU in 1 L
Postop day 6	Drain abdominal cavity as completely as possible and remove Tenckhoff catheter.			

*Approximately 4 weeks separate cycles of intraperitoneal chemotherapy; drugs are instilled through a soft catheter positioned by paracentesis. Mit C = mitomycin C, 5-FU = 5-fluorouracil.

age, damage to vital structures and an unsatisfactory surgical result. When tumours are invasive, dissection must be carried onto normal tissue. For low-grade lesions, it is adequate and safe, constituting acceptable principles of surgical oncology, to remove the tumour through the interface of normal and tumour tissue. However, when the tumour is of moderate- or high-grade malignancy, reasonable palliation can sometimes be achieved and long-term survival may result if distant metastasis does not occur. Cytoreductive surgery should be accompanied by intraperitoneal chemotherapy because satisfactory palliation or long-term disease-free survival was not achieved without it.

The Roswell Park group[5] had excellent results when they used intraperitoneal cis-platinum chemotherapy in patients with ovarian cancer who had intra-abdominal tumour nodules 1 cm in diameter or smaller. A group from the Netherlands[6] obtained good responses in patients treated with mitomycin C when there were only small tumour nodules in the abdominal cavity. We[7] had good results with cytoreductive surgery plus intraperitoneal 5-fluorouracil and mitomycin C in patients who had malignant mucinous adenocarcinoma of colonic or appendiceal origin. Intraperitoneal chemotherapy in the presence of small-volume tumour may benefit patients with malignant disease disseminated throughout the peritoneal cavity.[1]

In selecting patients for cytoreductive surgery, certain factors must be considered. With moderate- or high-grade tumour, the long-term disease-free survival is usually limited and metastases may occur at other sites, causing death. In these patients, the standard surgical indications for palliative surgery (intestinal obstruction or uncontrollable abdominal distension from tumour or ascites) should be the indications for surgery.

Malignant pseudomyxoma peritonei will never metastasize, so, if the tumour is removed from the abdominal cavity, these patients can be cured; the indication for cytoreductive surgery is the presence of the tumour itself, not any associated symptoms. Patients with pseudomyxoma peritonei may be expected to have a good prognosis with this treatment plan.

Patients with colonic adenocarcinoma of the mucinous histologic type were also treated in this series. This tumour is locally more invasive, so that a complete cytoreduction is more difficult. Also, residual tumour is more solid and has a well-developed vasculature. This means that tumour penetration by chemotherapy will not be as great as with malignant pseudomyxoma peritonei. When tumour cells are suspended in an avascular protein gel (mucinous ascites), the chemotherapy diffuses into the mass, is not metabolized or removed and may be expected to exert maximal

Table IV. Results of Treatment of Patients With Peritoneal Carcinomatosis

	Group			
Result	**1**	**2**	**3**	**4**
No. of patients	18	17	8	4
NED after operation	11	7	3	1
Primary site				
Appendix	17	6	1	1
Colon	0	11	7	3
Unknown	1	–	–	–
Symptoms/signs				
Bowel obstruction	3	5	5	2
Massive ascites	8	5	2	0
Abdominal mass	3	4	0	1
Rising CEA	4	3	1	1
Complications after cytoreductive surgery*				
Peritonitis	3	3	0	0
Bowel perforation	2	2	6	0
Prolonged ileus	2	3	1	0
Abscess	2	0	0	0
Intraperitoneal chemotherapy/no intraperitoneal chemotherapy	13/5	14/3	3/5	4/0
NED	9/2†	6/0	3/0	1/0
AWD	2/0	5/1	0/0	0/0
DOD	0/2	3/2	0/4	2/0
DOC	2/1	0/0	0/1‡	1/0

NED = no evidence of disease, CEA = carcinoembryonic antigen, AWD = alive with disease, DOD = died of disease, DOC = died of other causes.
*One patient died of staphylococcal pneumonia.
†Both patients received 15 cycles of γ-interferon intraperitoneally; they were the only ones in the series who had no evidence of disease in the absence of intraperitoneal chemotherapy.
‡Died with multiple small-bowel perforations.

cell kill. Well-vascularized tumour nodules and normal structures rapidly remove chemotherapeutic agents by lymphatic channels and the capillary network. In summary, one expects intraperitoneal chemotherapy to produce its greatest cell kill when the tumour is avascular. This is just the opposite of chemotherapy given by the intravenous route.

Even though mucinous colonic adenocarcinoma may invade intra-abdominal structures and implant widely on all peritoneal surfaces, it rarely metastases by lymphatic or hematogenous routes. By the theories of metastases suggested by Weiss,[8] this tumour would have a metastatic inefficiency of infinity.

One may question the use of the ball-tipped electrocautery on pure cut at high voltage. Its advantages are speed, accuracy of dissection and hemostasis. A large amount of tumour tissue can be removed rapidly at one session, without the extensive blood loss that results from sharp dissection. Even the smallest amount of blood in the operative field will interfere with exposure and may result in damage to vital structures. Unless large vessels are transected, the electrocautery maintains absolute hemostasis and cleanly defines the plane of dissection between tumour and normal tissue. Early in the course of his experience, the surgeon will recognize the characteristic features seen when transecting tumour, fat, abdominal adhesions or vital structures.

Long-term (3 years) disease-free survival was seen in the majority of patients with nonmetastasizing tumour in this series. These clinical data suggest that a combination of cytoreductive surgery with the ball-tipped electrocautery on pure cut at high voltage followed by intraperitoneal chemotherapy can cure selected patients with malignant large-bowel cancer on peritoneal surfaces.

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SESAP VI Critique

Item 105

Hyperchloremic metabolic acidosis is a recognized complication of diverting urine through an ileal segment. The problem occurs with varied incidence after construction of an ileal or colonic conduit, a continent ileal pouch, or a ureterosigmoidostomy. It may be seen in patients with normal renal function and in the absence of systemic electrolyte changes. Hyperkalemic, hypochloremic metabolic acidosis can occur when jejunal rather than ileal segments are used for urinary diversion.

Physiologic explanations of hyperchloremic metabolic acidosis include: selective reabsorption of urinary chloride by the ileal mucosa; a renal acidifying defect; reabsorption of ammonium chloride, and bicarbonate secretion by the colon in response to local introduction of urine.

The absence of significant changes in serum chloride or total CO_2 should not be equated with an absence of metabolic abnormalities after urinary diversion. Therapy for hyperchloremic metabolic acidosis must include restriction of chloride intake, because of the relationship between chloride reabsorption and acid reabsorption.

B

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Periosteal Neochondrogenesis for Biologically Resurfacing Joints: Its Cellular Origin

Rick Zarnett, MD, MSc;* Robert B. Salter, OC, MD, FRCSC†

The purpose of this study was to determine if the hyaline-like cartilage produced in major full-thickness defects of a joint surface, treated by a free periosteal graft and subjected to continuous passive motion (CPM), originated exclusively from the progenitor cells of the cambium of the graft. Free periosteal grafts were raised from the tibia of both hind legs of eight male New Zealand rabbits and transplanted into full-thickness defects across the entire width of the patellar groove of 15 female rabbits. Postoperatively, CPM was instituted and the animals were sacrificed after 3 weeks. Cells from the regenerated tissue were grown from tissue explants and their karyotypes determined. In 33% of the rabbits, all cells contained a Y (male) chromosome, indicating that regenerated tissue originated exclusively from the progenitor cell of the periosteal graft. Karyotypes of the cells from the other 67% were mosaics (both female and male); thus, their cellular origin was from both the periosteal allograft and the pluripotential mesenchymal cells in the subchondral tissues.

Le but de la présente étude consistait à déterminer si le cartilage de type hyalin, qui apparaît quand des dysplasies interarticulaires majeurs sont traitées par greffe périostique libre et soumises à une mobilisation passive continue (MPC), provient exclusivement des cellules souches du cambium du greffon. Ces greffons ont été obtenus à partir des tibias des membres inférieurs de huit lapins New Zealand mâles. Ils ont été transplantés chez 15 lapines, dans des dysplasies complètes sur toute la largeur de la gouttière rotulienne. Après l'opération, une MPC fut mise en place et les animaux furent sacrifiés après 3 semaines. Les cellules du tissu regénéré furent mises en culture et leurs karyotypes furent déterminés. Chez 33% des lapines, toutes les cellules contenaient le chromosome Y (mâle), indiquant que le tissu de regénération provenait exclusivement des cellules du greffon périostique. Le karyotype des cellules des 67% restant était constitué d'une mosaïque (mâle et femelle); en conséquence, leur origine cellulaire venait, à la fois, de l'allogreffe périostique et des cellules mésenchymateuses pluripotentes du tissu sous-chondral.

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Prosthetic joint replacement is a major advance in the treatment of degenerative joint disease, but possible residual loosening and infection make the procedure unacceptable in the young or active person.

Recent investigations[1-3] at our research laboratory demonstrated that major, full-thickness defects in a joint surface can be "biologically resurfaced" by stimulating the cambium of free periosteal grafts with continuous passive motion (CPM).

In a previous study,[4] free autogenous periosteal grafts were labelled with tritiated thymidine to determine if the cellular origin of the hyaline-like cartilage was progenitor cells of the periosteal graft. This method enabled us to follow the pluripotential cells of the cambial layer of the grafts as they passed through the stages of neochondrogenesis. We were able to conclude that the thymidine-labelled cells in the regenerated tissue had originated from the periosteal graft. We were, however, unable to comment on the origin of the entire mass of regenerated tissue.

The rabbit has 22 pairs of chromosomes.[5,6] The 21 pairs of autosomes can be arranged in descending order of length and numbered serially (Fig. 1). Chromosome pairs 20 and 21 are the shortest acrocentric chromosomes, corresponding to group G in the human karyotype. The acrocentric Y chromosome is the smallest of the ka-

ryotype and can be placed in a morphologic group with chromosome pairs 20 and 21.[5,6] Thus, it is possible to differentiate between the karyotype of a female and a male cell by establishing if four or five small acrocentric chromosomes are present.

If an allograft of periosteum could be transplanted from a male to a female rabbit, the cells derived from the pluripotential cells of the cambial layer of the periosteum would carry a recognizable label (i.e., the Y chromosome). This label would not become diluted as the cells underwent subsequent mitosis.

This experiment was designed to answer the following question: Does the entire regenerated hyaline-like tissue originate from the progenitor cells of the periosteal graft or do the subchondral tissues provide pluripotential cells which contribute to the "biological resurfacing" of these major, full-thickness defects?

Material and Methods

Twenty-three (15 female, 8 male) adolescent, New Zealand rabbits, weighing between 2.2 and 2.8 kg, were used as models. The surgical procedures were performed under general anesthesia induced by an intravenous injection of sodium pentobarbital (25 mg/kg body weight) and maintained by an inhalation mixture of 1% halothane, 60% nitrous oxide and 39% oxygen.

In the male rabbit, the skin of the hind limbs was shaved from the hip to the ankle and prepared with povidone-iodine. A medial skin incision (6 cm long) was made over the proximal tibia, and a rectangular incision 7.5 × 15 mm was made in the underlying periosteum of both hind limbs. The periosteal graft was carefully elevated from the underlying tibia by sharp subperiosteal dissection, and to distinguish the two individual layers of periosteum a blue 5-0 polypropylene suture was placed in the fibrous layer of each graft. The grafts were placed in 0.9% sterile saline solution until transplantation.

Each female rabbit was anesthetized and the appropriate limb prepared as in the donor. A medial arthrotomy of one knee joint was performed on each rabbit. The patella was dislocated laterally and the allograft of periosteum transplanted into a 5-mm full-thickness defect across the entire patellar groove, as previously described[3,4] (Fig. 2).

While under anesthesia, the animals were placed on the CPM apparatus where they remained until they were killed 3 weeks later.[7]

Tissue Culture

The involved knee joints were exposed under sterile conditions. A portion of the newly formed tissue from the patellar groove was removed and placed in a Petri dish containing cold sterile phosphate-buffered saline (PBS). The sample was obtained from the centre of the defect, well above the underlying subchondral bone, in order to avoid contamination by the surrounding host (female) tissue.

To confirm the biopsy location, 50% of the knees (randomly selected) were fixed, decalcified and stained as previously described.[4] This allowed us to observe any signs of graft rejection.

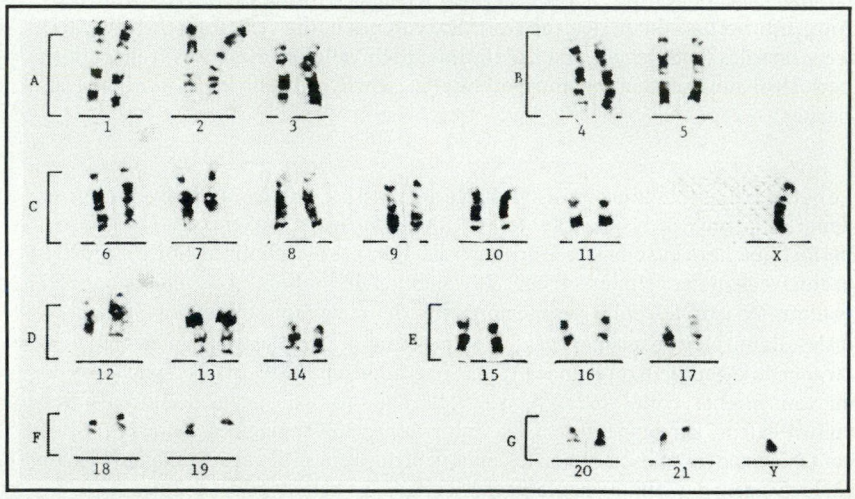

FIG. 1. Karyotype of rabbit contains 22 pairs of chromosomes. As in human, male contains five small acrocentric chromosomes (pairs 20 and 21 plus Y). In contrast, female has only four small acrocentric chromosomes (pairs 20 and 21).

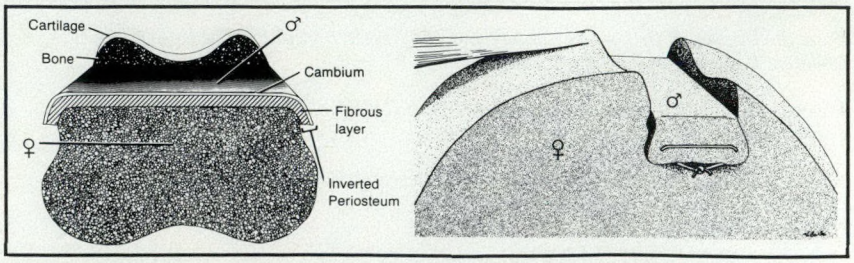

FIG. 2. (Left) Transverse section through male periosteal allograft lying on subchondral bone. Cambium of graft faces into joint. Base of defect is flat in contrast to contour of patellar groove. (Right) Lateral view of periosteal graft sutured to periosteum of femur. Depth of defect varied from 2 mm in centre of groove to 5 mm at edge.

The tissue sample was transferred to a sterile Petri dish with 3 to 4 ml of medium, consisting of alpha minimal essential medium (MEM) supplemented with 15% fetal calf serum (FCS), penicillin (100 units/ml), streptomycin (100 mg/ml) and amphotericin B (2.5 μg/ml). The tissue was then cut into pieces approximately 0.5 mm^2 and 6 to 10 pieces were transferred to each of four Falcon plastic culture flasks. The flasks were placed upright for 30 minutes in the incubator to allow the tissue explants to attach firmly to the flasks. With 10 ml of medium the explants were incubated at 37°C in 95% humidified air plus 5% carbon dioxide. The medium was changed twice weekly.

Subculture Technique

At 4 to 6 weeks, the cells were separated from the flasks with 0.25% trypsin/ethylene diamine tetra-acetic acid, and secondary cultures were established on sterile glass microscope slides, which were placed in culture dishes and incubated for a further 48 hours.

Harvesting of Chromosomes

After the 48 hours, colcemid (concentration 0.67 μg/ml) was added to the medium and the Petri dishes were incubated for 3 more hours, after which the medium was removed and the cells were hypotonically expanded using 0.075 M potassium chloride.

Fixing the Cells

Ten millilitres of a 3:1 mixture of ice-cold methanol and glacial acetic acid were slowly added to the dishes, allowing the cells to fix for 15 minutes. This procedure was repeated three times. The cells were spread and flattened on the glass slides and the chromosomes were then stained with Giemsa solution.

Examination for Chromosomes

The slides were screened under low power (125×) and chromosome spreads identified for counting and photography. When a cell in which all the chromosomes were clearly defined was identified, it was examined further under high power (1250×) and the number of acrocentric chromosomes (four indicating a female karyotype and five indicating a male karyotype) documented.

Results

Tissues from the transplanted knees of the 15 female rabbits were studied. The first four rabbits made up a pilot group; their knees were examined for evidence of graft rejection. Of the remaining 11 rabbits, 1 was excluded because of a dislocated patella and 1 because the periosteal graft had become detached from the subchondral bed. This left nine animals for chromosomal analysis of the regenerated tissue.

Gross Findings

In all rabbits, the patellar groove was fully restored; the defects were filled in by smooth tissue resembling hyaline articular cartilage. There was no evidence of graft rejection.

Histologic Findings

The surface of the regenerated tissue was smooth and resembled hyaline articular cartilage. Round chondrocytes were contained in well-formed lacunae. The extracellular matrix stained well with Safranin O, indicating glycosaminoglycan production.

After 3 weeks of CPM there was no histologic evidence of graft rejection or cellular infiltration in the regenerated tissue.

Tissue samples from four knees were examined histologically. The sample was always taken from the central and superficial area of the graft, thus avoiding both the regenerated tissue in the base of the defect and the normal articular cartilage.

Chromosomal Analysis

The tissue explants grew slowly; it took 4 to 6 weeks for a sufficient number of cells to be available for subculture. A minimum of two flasks containing between 6 and 10 tissue explants each were examined to give a wide sampling of tissue. The karyotypes of 194 cells were determined (average 21.6 cells/rabbit).

In three of the nine female rabbits, 100% of the cells examined carried the male karyotype, proving that all these cells had differentiated from the pluripotential cells in the cambium of the periosteal graft (Fig. 3). In the other six rabbits, the karyotypes were sexual mosaics, containing both female (host) and male (graft) cells (Fig. 4).

Discussion

In their original investigation on the "biological resurfacing" of joints, O'Driscoll and colleagues[3] reported that in 20% of the control animals (i.e., those that did not receive a periosteal graft), hyaline cartilage was the predominant tissue formed. In addition, 1-mm full-thickness defects are capable of

healing with hyaline-like cartilage when stimulated by CPM.[8] Therefore, the subchondral tissues can produce hyaline-like cartilage, although it is inferior in quantity and quality to the tissue formed when full-thickness defects are grafted with periosteum.[9]

The present investigation demonstrated that the hyaline-like cartilage produced when free periosteal grafts are transplanted into full-thickness defects is not derived entirely from the periosteal graft; in 67% of rabbits the regenerated tissue had a cellular origin from both periosteal graft and the subchondral tissues. In the remaining 33% the periosteal graft was exclusively responsible for the cellular origin of the regenerated tissue.

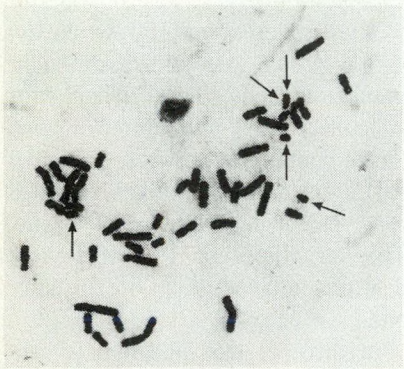

FIG. 3. Photomicrograph of chromosomal spread contains five small acrocentric chromosomes (arrows), proving that it originated from periosteal graft.

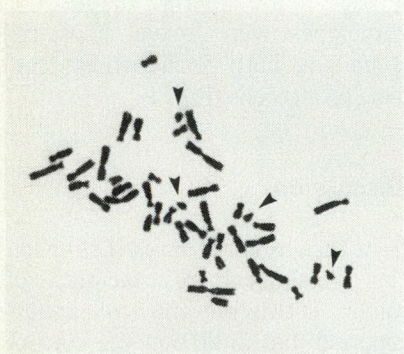

FIG. 4. This cell contains four small acrocentric chromosomes (arrows) and is therefore female. It has its origin from undifferentiated mesenchymal cells in subchondral tissues.

Early attempts at "biological resurfacing" failed because the tissues underwent either necrosis and degeneration or, at best, conversion to fibrous tissue.[10] Hoover and Coventry[11] believed that the various interposition materials acted only as a culture medium and had no effect on the ultimate repair tissue on the joint surface. Ruback and associates[9] placed a cell-impenetrable filter between the cancellous bone and a periosteal graft in an attempt to demonstrate the origin of the cartilage-like tissue regenerated in their experimental model. At 4 to 8 weeks, all the filters had fractured, making the contribution to the repair tissue from the underlying bone difficult to assess. Because the cells represented clonal outgrowths from tissue explants, the proportion of male and female cells is an unreliable indicator of the actual proportion of tissue derived from each of the two sources.

We demonstrated that the hyaline-like cartilage, either totally or in part, originates from the periosteal graft. Thus, the periosteum is of primary importance in this "biological resurfacing" model.

Conclusions

The hyaline-like cartilage produced when a free periosteal graft is transplanted into a major full-thickness articular defect in a joint surface and subjected to continuous passive motion, is derived either totally or in part from the periosteal graft. In two-thirds of the animals in this study, the subchondral tissues provided pluripotential cells contributing to neochondrogenesis.

We thank Mr. Ajai Kumar and Mrs. Chin Ho for technical assistance. This research project was approved by the Animal Experimentation Committee at The Research Institute, The Hospital for Sick Children, Toronto.

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Does Endoscopy Really Help the Surgeon Evaluate Gastric Cancer?

Nadey S. Hakim, MD, FRCS; Michael G. Sarr, MD, FACS; Jon A. van Heerden, MD, FRCSC

To determine whether gastroscopy helps the surgeon in preoperative planning and decision-making in patients with gastric cancer, the authors reviewed the charts of 100 consecutive patients with surgically proven gastric cancer. The findings from gastroscopy, upper gastrointestinal series and computed tomography were evaluated for their ability to define the anatomic site of the lesion, proximal and distal extent of gastric involvement, presence of a mass or ulceration and the sensitivity of diagnosis. The sensitivity of endoscopic biopsy and brush cytology were also determined. Gastroscopy was found to be the most sensitive diagnostic test, both in recognizing the presence of an abnormality (100% versus 86% versus 76% respectively) and the possibility of a malignant condition (88% versus 71% versus 76%); in addition, endoscopic biopsy and brush cytology were diagnostic in 90% and 70% of patients, respectively. Gastroscopy and upper gastrointestinal series were equally accurate in determining proximal or distal extent of tumour. The authors concluded that gastroscopy is the most sensitive diagnostic test in patients with gastric cancer; upper gastrointestinal series does not add significantly useful information to the preoperative evaluation. Computed tomography can assess regional and distant metastasis, but its contribution as to the local extent of the tumour is limited.

Les auteurs ont étudié les dossiers médicaux de 100 patients consécutifs porteurs de cancers gastriques démontrés à la chirurgie, afin d'établir si, dans le cancer gastrique, la gastroscopie aidait le chirurgien dans sa planification préopératoire et dans sa prise de décision. Les résultats des examens de gastroscopie, des clichés en série des voies digestives hautes et de la tomodensitométrie ont été mis en parallèle pour établir leur capacité de définir le siège de la tumeur, l'étendue proximale et distale de l'atteinte gastrique, la présence d'une masse ou d'ulcération et la sensibilité diagnostique. On a aussi déterminé la sensibilité de la biopsie endoscopique et de l'examen cytologique par brossage. La gastroscopie s'est avérée le test diagnostique le plus sensible, tant pour reconnaître la présence d'une anomalie (100% contre 86% et 76%, respectivement), que pour prévoir la possibilité qu'il s'agisse d'une affection maligne (88% contre 71% et 76%); la biopsie endoscopique et la cytologie par brossage avaient une valeur diagnostique chez 90% et 70% des patients, respectivement. La gastroscopie et les clichés en série des voies digestives supérieures étaient d'une égale précision pour déterminer l'étendue proximale et distale de la tumeur. Les auteurs concluent que la gastroscopie représente l'instrument diagnostique le plus sensible dans les cas de cancer de l'estomac; les clichés en série des voies digestives n'ajoutent pas vraiment d'information utile à l'évaluation préopératoire. La tomodensitométrie peut évaluer les métastases régionales et à distance, mais sa contribution à l'évaluation de l'étendue locale est limitée.

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Flexible fiberoptic gastrointestinal endoscopy has become a well-established procedure for evaluating the esophagus, stomach and duodenum. In several studies[1-4] the diagnostic accuracy of radiologic contrast examination of the upper intestine has been compared with endoscopic techniques. Contrast roentgenography was found to be accurate in at least 90% of patients, and several authors[3,4] have advised that endoscopic examination be reserved for patients in whom the results of radiologic assessment are inconclusive or when a histologic diagnosis of malignancy is required.

The purpose of this study was to compare, retrospectively, the accuracy of gastroscopy, conventional upper gastrointestinal roentgenography and computed tomography and to correlate results with surgical findings and the final pathology report, in patients with proven gastric carcinoma. Our aim was to determine if any of the tests provide more information than others to assist the surgeon in planning operative strategy.

Methods

One hundred consecutive patients seen at the Mayo Clinic between 1985 and 1987 with surgically confirmed gastric cancer were studied retrospectively. Only those who underwent preoperative gastroscopy carried out by a member of our group were included. The results of endoscopy and the histopathologic report of biopsies or cytologic study were taken from the original records. The findings of upper gastrointestinal contrast roentgenography and computed

tomography, when performed in addition to the endoscopy, were also reviewed. Each diagnostic investigation was assessed for its ability to recognize one or more of the following: a gastric abnormality defining accurately the macroscopic appearance (benign versus malignant); the presence or absence of mass or ulceration; the site (upper third or lower third of stomach) and size of the lesion; the gross margins of the lesion (proximal extension in relation to the esophagogastric junction and distal extension in relation to the pylorus) and the distensibility of the stomach. Biopsies and brush cytologic samples taken during endoscopy were reviewed for diagnostic sensitivity.

Results

The mean age of the group was 69 years and the ratio of men to women was 4 to 1. Thirty-five patients underwent an upper gastrointestinal series and 34 abdominal computed tomography, in parallel with the gastroscopy.

Ninety-eight patients underwent gastrectomy, 1 had a bypass for palliation and in the other the tumour was deemed unresectable. All had an adenocarcinoma of the stomach.

The results of the three diagnostic procedures are shown in Table I.

With respect to gastroscopy, the distensibility of the stomach was mentioned in only seven reports and was correct in all cases. Multiple biopsies were performed in all cases and the accuracy in diagnosing malignancy was 90%; thus, 10% of biopsy results were false negatives. Brush cytology, performed concomitantly in 25% of cases, gave positive results in 70%.

Of the 35 upper gastrointestinal series, 5 (14%) were interpreted as being normal (false negative). The orientation (anterior, posterior, lesser and greater curvature) was rarely mentioned and the distensibility of the stomach was never mentioned.

Of the 34 computed tomograms, abnormal features suggestive of a malignant lesion were detected in 26 (76%). Thickening of the gastric wall was noted in 15 patients (45%) and was the most common indication of malignant disease. The other abnormal scans showed, in addition, a mass within the stomach. Although the examination was accurate in defining the site of the lesion, its extent was poorly assessed. In patients with metastatic nodal disease the positive scans revealed local lymph-node enlargement in nine. Thus, the sensitivity of recognition of nodal metastases was 9 of 20 (45%), whereas the specificity approached 100%. Liver metastases were incorrectly suggested in one patient.

Discussion

Our study clearly demonstrates that gastroscopy with biopsy is a sensitive diagnostic procedure (90%), which provides an objective diagnosis of gastric cancer in patients with proven carcinoma of the stomach. Endoscopy identifies mucosal abnormalities related to gastric cancer with greater sensitivity (100%) than either gastrointestinal contrast studies (86%) or computed tomography (76%). Gastroscopy and gastrointestinal contrast studies were equally accurate in determining proximal and distal extent of the malignant disease. Computed tomography may provide information concerning the presence or absence of liver metastases and nodal involvement, but did not provide additional information on the local extent of the tumour.

In the past, the upper gastrointestinal series has been the "gold standard" against which to judge the diagnostic accuracy of tests for gastric cancer; introduction of the air contrast technique in Japan further improved its sensitivity, often allowing the diagnosis of superficial, early gastric cancers. However, the advent and rapid adoption of gastroscopy in the 1970s added a new dimension to the diagnostic armamentarium; surgeons are now asked to see many patients with endoscopically suspected (or proven) gastric cancer who have not undergone conventional contrast roentgenography. Before we carried out this study, our hypothesis, based on a subjective impression and now proven incorrect, was that upper gastrointestinal contrast studies were more accurate in determining the extent of the malignant disease, and, therefore, were helpful in aiding the planning of the operative procedure. Also, we confirmed the findings of several other studies[2,3,5] that gastroscopy was a very sensitive method for

Table I. Diagnostic Procedures for Evaluating Gastric Carcinoma

Procedure	Abnormal findings, %	Macroscopic impression of carcinoma, %	Site and orientation, %	Presence or absence of ulceration, %	Presence or absence of mass, %	Proximal/distal extent of malignancy, %	Biopsy, %	Brush cytology, %
Gastroscopy (n = 100)	100	88	95	96	82	89	100 (90 +ve)	25 (70 +ve)
Upper gastrointestinal contrast roentgenography (n = 35)	86	71	77	95	77	91	–	–
Computed tomography (n = 26)	76	76	100	–	76	–	–	–

diagnosing gastric carcinoma. It is, in our experience, superior to contrast studies in sensitivity and equally efficacious in delineating the proximal and distal extent of the lesion. Moreover, gastroscopy provides the ability to obtain an objective diagnosis of a malignant condition through direct biopsy or by cytologic examination. Biopsies were diagnostic in 90% of cases, a rate similar to the sensitivity reported by others,[6] and brush cytology was diagnostic in 70%, which is substantially less than the 83% reported by Pilotti and colleagues.[6]

Whether, by combining endoscopy and conventional radiologic contrast study, diagnostic sensitivity is improved markedly and is thus cost effective, is difficult to answer. Of the 10 patients in whom the endoscopic biopsy gave a false-negative result, 6 had lesions that the endoscopist described as highly suggestive of a malignant condition, and in the other 4 the lesions were abnormal but equivocal with respect to malignancy. Of these four patients, three had abnormalities on radiologic contrast study which could have been considered suggestive of a malignant lesion; therefore the combined use of the two diagnostic tests might have benefited only three patients. Moreover, since radiologic contrast studies are no more accurate in delineating proximal or distal tumour extension, we conclude that they offer little additional preoperative information of importance to the surgeon when gastric cancer is suspected on endoscopic examination or proven by additional biopsy.

Two fundamental types of gastric computed tomography are performed in clinical practice: (a) the directed examination, prompted by a history of known or suspected gastric disease based on previous surgery, endoscopy or barium study and (b) the incidental examination in which the stomach is studied as part of a more general search for intra-abdominal disease, when no known gastric disease exists. In our study, all such scans were directed studies, ordered when there was a suggestion of an abnormality on endoscopy or contrast roentgenography. In spite of this, there were false-negative results in 24% of cases. Had they not been "directed" tests, the sensitivity most likely would have been less. In several reported series,[7–9] wall thickness 1 cm or greater has been a reliable indicator of gastric malignant disease. Little information was available to assess the local extent of the tumour. None of the 26 patients who had computed tomography were found to have liver metastases at surgery and in only one scan was there a suspicion of hepatic involvement.

Conclusions

Our study suggests that in the investigation of gastric disease, the routine use of upper gastrointestinal contrast roentgenography with only selective use of gastroscopy may reduce the number of endoscopic examinations but sacrifices diagnostic sensitivity and would be unacceptable. Gastroscopy, therefore, is the examination of choice in the patient with suspected gastric cancer; contrast roentgenography should be performed as a second choice. On the other hand, gastroscopy is not necessarily indicated in the patient who has a mass that appears malignant on contrast study, unless operation will only be undertaken if there is objective documentation of malignancy (i.e., biopsy proof). Computed tomography can assess the presence of regional node metastases, with a sensitivity of 45%, and possibly the absence of liver metastases but does not add important information on the local extent of the tumour.

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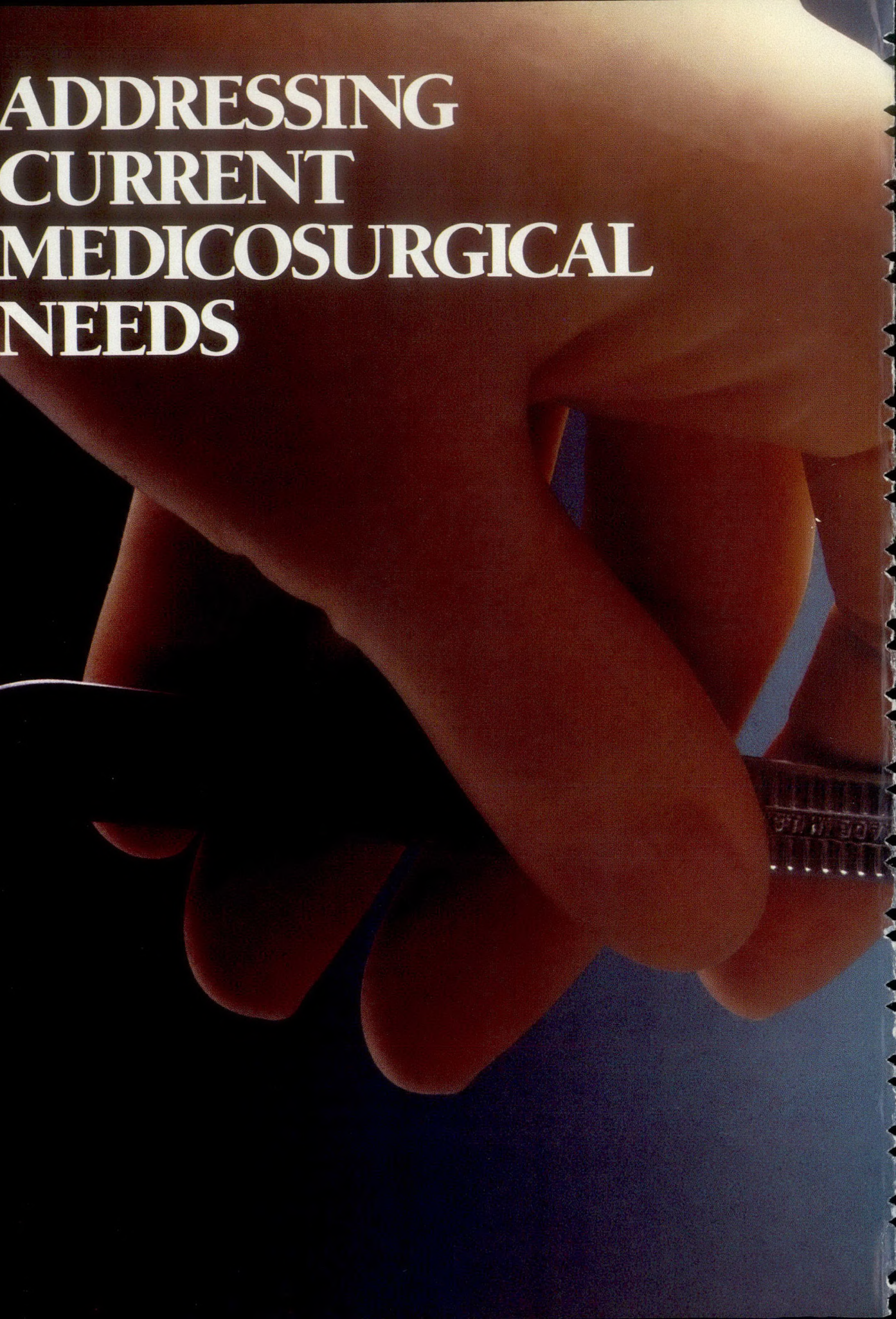
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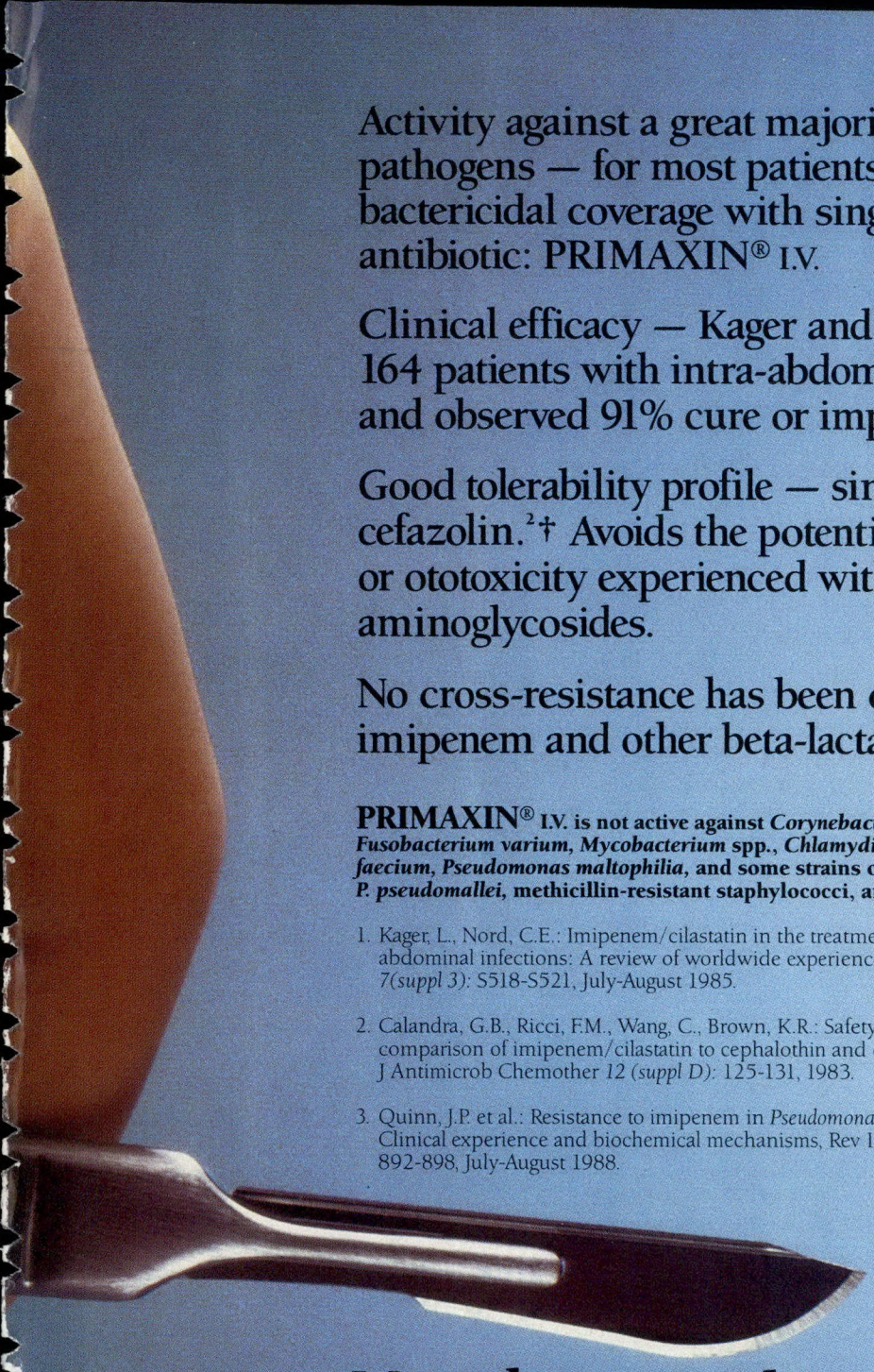

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Comparison of Processed Bovine Internal Mammary Arteries and Autologous Veins as Arterial Femoral Substitutes in Dogs: Blood Compatibility and Pathological Characteristics

F.J. Teijeira, MD, PhD; Yves Marois, MSc; L. Aguiar, MD; R. Guidoin, PhD; R. Bauset, MD; G. Lamoureux, MD; A. Downs, MD, FRCSC;* M. Marois, MD; D. Boyer, MSc

This study was undertaken to compare the chemically processed internal mammary artery (BIMA) and the autologous femoral vein as arterial grafts. The BIMA prosthesis was implanted as a left femoral artery bypass and the femoral vein as a right femoral artery bypass graft in 27 dogs. In groups of three dogs the grafts were implanted for predetermined durations: 4, 24 and 48 hours (short term), 1, 2 and 4 weeks (medium term) and 3, 6 and 9 months (long term). All autologous veins were patent when the dogs were killed. The patency rates of the BIMA grafts were 100% in the short-term group, 67% in the medium-term group and 29% in the long-term group. The deposition of labelled fibrinogen and platelets on flow surfaces, the structural preservation of the wall of the BIMA prosthesis and accumulation of thrombi during the period of implantation were studied.

Cette étude a été entreprise dans le but de comparer l'artère mammaire interne bovine traitée chimiquement (BIMA) et la veine fémorale autologue utilisées comme greffons artériels. La prothèse BIMA a été greffée chez 27 chiens comme dérivation de l'artère fémorale gauche alors que la veine fémorale était utilisée pour ponter l'artère fémorale droite. Les animaux, répartis par groupes de trois chiens, ont reçu les greffes pour des durées prédéterminées de 4, 24 ou 48 heures (le court terme), de 1, 2 ou 4 semaines (le moyen terme) et de 3, 6 ou 9 mois (le long terme). Quand les animaux furent sacrifiés, toutes les veines autologues étaient perméables. Le taux de perméabilité des greffons BIMA était de 100% à court terme, de 67% à moyen terme et de 29% à long terme. Ont aussi fait l'object d'une étude, le dépot de fibrinogene marqué et de plaquettes sur la surface luminale, la préservation de la structure de la paroi de la prothèse BIMA et l'accumulation de thrombi durant la période d'implantation.

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Chemically processed grafts are used as substitute blood conduits in peripheral vascular surgery when autologous vein is not available. Although human umbilical veins have performed satisfactorily for some[1,2] and outstandingly for others,[3] several authors[4,5] have questioned their durability. Bovine heterografts (originating from carotid arteries) are now used only as a secondary vascular access;[6-8] their primary use in peripheral vascular surgery was practically abandoned after reports of early thrombosis and aneurysm formation.[9-11] Their secondary use is now being challenged by the polytetrafluoroethylene graft.[12,13]

Despite marginal improvements, bovine grafts have been disappointing clinically.[14-16] Nevertheless, chemically processed biologic grafts of small diameter are still being investigated. New ideas led Malone and colleagues[17] to develop an acellular matrix biograft, and Loisance and colleagues[18] described a new biochemical processing of human placental arteries. In Brazil, Biocor Industrias[19] explored the possibilities of a chemically processed bovine internal mammary artery (BIMA) as a vascular substitute for small- and medium-sized arteries. Although results in humans were satisfactory,[19] more, thorough investigation must be done before its

final commercial release. We report our in-vivo evaluation of this new graft as a femoral artery substitute in the dog. The BIMA prosthesis was compared with the autologous femoral vein with respect to patency, morphologic features and platelet and fibrinogen deposition on the luminal surface of the graft placed for predetermined periods.

Materials and Methods

The Grafts

The BIMA prostheses (Fig. 1) were obtained from Biocor Industrias Ltda of Nova Lima, Brazil. The bovine internal mammary artery graft is chemically processed with glutaraldehyde for 3 months, then stored in sterile buffered 3% formaldehyde solution. It must therefore be abundantly and carefully rinsed in heparinized saline before implantation.

Autologous femoral veins were dissected during surgery in each dog and were interposed as arterial femoral substitutes.

Platelet Labelling

Whole blood (50 ml) was withdrawn from each study dog after a 24-hour fast. Platelets were isolated by double centrifugation and labelled with indium-111 oxinate (Mallinkrodt Canada Inc., Montreal, PQ) using a method that was modified from the one described by Thakur and colleagues.[20] The platelets were labelled with 300 to 700 μCi of ^{111}In by incubation. They were washed in saline and resuspended in autologous plasma. Labelling efficiency was typically around 85%, but no viability test was done.

Graft Implantation and Reoperation

Twenty-seven mongrel dogs, weighing on average 20 kg, were selected as stipulated by the Canadian Council on Animal Care. After a 24-hour fast, they were anesthetized with 25 mg/kg of intravenous Pentothal and then mechanically ventilated. Under strict sterile conditions, segments from both right and left femoral arteries were removed and the right femoral vein was harvested. In each case, a few minutes after injection of 1 mg/kg of heparin intravenously, 5 cm of autologous femoral vein was interposed as a graft in the right femoral artery and the 5 cm of BIMA graft in the left femoral artery. End-to-side or end-to-end anastomoses were performed using Prolene (Ethicon Ltd., Peterborough, Ont.) 6-0 or 7-0 suture. The dogs were given 15 000 units of prolonged-effect antibiotic (Penlong S; Rogar STB Inc., Montreal, PQ), returned to their cages and fed a normal diet. A second operation was carried out at predetermined intervals — 4, 24 and 48 hours (short term), 1, 2 and 4 weeks (medium term) and 3, 6 and 9 months (long term) — for exposure to labelled platelets and fibrinogen. Overall, nine groups of three dogs per duration of implantation were evaluated. Those in the long-term group underwent angiography before the second operation.

Investigations

The dogs remained anesthetized for 4 hours after intravenous injection of platelets, labelled in the laboratory, and 125 μCi of labelled ^{125}I fibrinogen. The grafts were then removed. Both venous and prosthetic grafts were gently rinsed in heparinized physiologic saline and immediately cut into five segments of equal length, the first and fifth segments including the anastomotic areas and the other three segments located in between. Each segment was counted separately for deposition of labelled platelets and fibrinogen in a well counter (Compu Gamma 1282; LKB-Wallac, Broma, Sweden). The measured activity, corrected for time and background, was expressed as net counts per minute to give a relative measure of the platelet and fibrinogen deposits along grafts.

The specimens were then fixed in a 1.5% buffered solution of glutar-

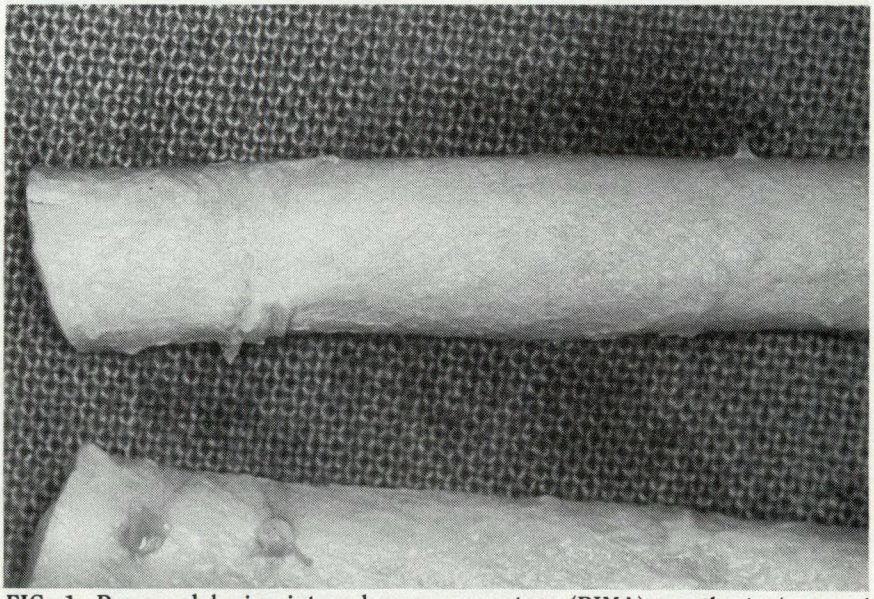

FIG. 1. Processed bovine internal mammary artery (BIMA) prosthesis (external diameter 6 mm, wall thickness 0.4 mm).

aldehyde and processed for light microscopy and scanning electron microscopy according to a previously described protocol.[21]

Statistical Analysis

Statistical analysis of the results was by analysis of variance, for repeated measures, using Fischer's LSD (least significant difference) for a posterior two-by-two comparison.

Results

Three dogs died for reasons not apparently related to the vascular surgery. Consequently, only 24 dogs were available for examination of patency, quantification of platelet and fibrinogen deposition and pathological investigation.

Patency

The patency rates are summarized in Table I. Patency of the BIMA grafts decreased with length of implantation, but all venous grafts were patent at the time of removal. Three dogs were withdrawn from the study because of generalized thrombosis: one in the short-term group and two in the long-term group. No aneurysmal formation was visible either in the BIMA grafts or the autologous veins.

Table I. Patency Rates of Bovine Internal Mammary Artery (BIMA) and Autologous Femoral Vein Grafts at Different Time Intervals After Implantation

Group	Patency, % (no./total no.)	
	BIMA	Femoral vein
Short term	100 (8/8)	100 (8/8)
Medium term	67 (6/9)	100 (9/9)
Long term	29 (2/7)	100 (7/7)

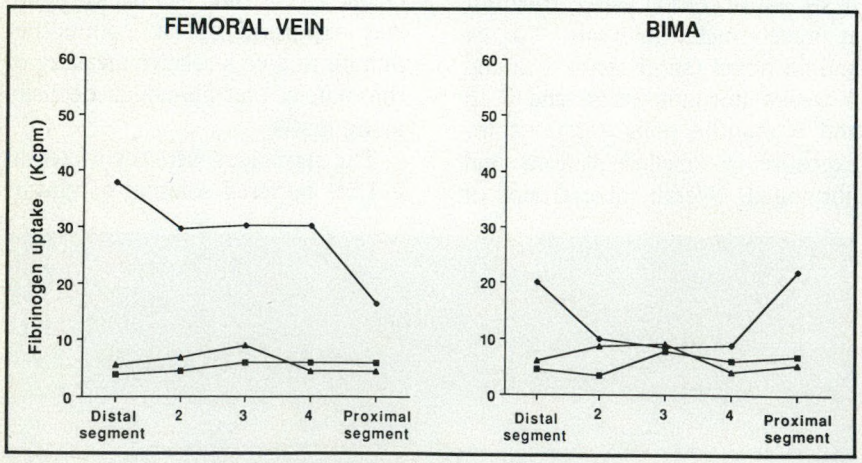

FIG. 2. Graphic representation of fibrinogen uptake along graft segment by BIMA grafts and autologous femoral veins for short- (diamonds), medium- (squares) and long-term (triangles) implantations. Kcpm = net counts per minute.

Fibrinogen and Platelet Uptake

Fibrinogen accumulation is shown in Table II. Analysis of fibrinogen uptake revealed significant increases ($p < 0.05$) in autologous vein grafts over the first 48 hours, and when compared with BIMA over the same period the latter finding was evident in every segment analysed except the proximal one, for which the difference was not significant. The fibrinogen uptake in the autologous vein grafts of the medium- and long-term groups was significantly ($p < 0.001$) lower than in the short-term group, but not statistically different from the uptake in the BIMA grafts.

Figure 2 illustrates the pattern of fibrinogen uptake by graft segments for each period of implantation. Uptake by autologous vein grafts was substantial at the distal anastomoses and along the middle segments in the short-term group, compared with the proximal anastomoses. Fibrinogen uptake by the BIMA grafts showed a selective increase at both distal and proximal anastomoses in the short-term group compared with the middle segments.

Platelet accumulation followed a similar pattern in that the increase

Table II. Fibrinogen Uptake (Net cpm) by BIMA and Autologous Femoral Vein Grafts

Graft	Implantation group	Graft segment				
		Distal	2	3	4	Proximal
Femoral vein	Short term	37 788	29 269	30 531	30 662	16 891
	Medium term	3 893	4 453	6 817	6 633	5 932
	Long term	5 119	6 953	9 175	4 893	4 858
BIMA	Short term	20 091	10 111	8 320	8 488	22 962
	Medium term	4 976	3 439	7 997	6 086	7 185
	Long term	5 705	8 686	8 843	4 644	5 689

was much greater in the autologous veins in the short-term group (Table III). Differences in pattern and intensity between the two materials were not statistically significant, probably because of the extreme variation in the viability of the platelets for each dog in the study. Figure 3 demonstrates clearly the accumulation of platelets at both anastomoses of the BIMA grafts in the short-term group.

Pathological Investigations

The structure of virgin BIMA grafts was observed by both light and scanning electron microscopy. The latter revealed a carefully processed graft whose defect-free surface was smooth, with a number of endothelial cells no longer viable. The basement membrane appeared to be well preserved, thus separating the blood flow from the underlying collagen matrix (Figs. 4 to 6). The wall was also well preserved and the tunica externa appeared normal.

After short-term implantation, accumulation of thrombotic matrix was visible for up to 2 weeks adjacent to the sutures at both anastomoses (Fig. 7). The middle segment of the flow surface was smooth with scattered deposits of fibrin platelets and erythrocytes. A discrete fibrosis of the media occurred with occasional displacement and restructuring of the internal elastic lamina.

After 1 month of implantation, the thrombi at the anastomoses of the BIMA grafts were organized and extended along the artery; the surface of the pannus exposed to the blood flow showed early reendothelialization. A few blood deposits were still evident in the medial part of the smooth luminal surface (Fig. 8). In the adventitia, granulomatous inflammatory tissue reacted to become incorporated with vasa vasorum.

In the patent grafts after long-term implantation, the pannus at both anastomoses exhibited a veil of newly formed endothelial-like cells. Flow surface appeared similar to that seen 1 month after implantation. Mild medial fibrosis was not noticeable, the elastic lamina was not always apparent and a granulomatous inflammatory reaction with foreign-body giant cells in the adventitia was seen (Figs. 9 and 10).

The structure of the femoral veins altered slightly shortly after implantation. For 2 weeks, thrombotic debris was visible at the anastomoses and over the flow surface (Fig. 11). Forty-eight hours later, intimal fibrosis occurred at both anastomoses where a partial denudation of the luminal surface was perceptible.

Between 1 week and 1 month, the subendothelial fibrosis became dense, with displacement and localized ruptures of the elastic network. Also, peripheral sclerosis was observed along the anastomoses after 1 month of implantation, at which time the thrombi had almost disappeared and the sutures were totally incorporated in the newly grown pannus, coated with endothelial cells. The middle portion of the graft still had some debris and was still partially denuded. Over the long term, surface cells proliferated sufficiently to cover the whole luminal surface (Fig. 12). The wall became thicker as a result of progressive fibrosis (Fig. 13).

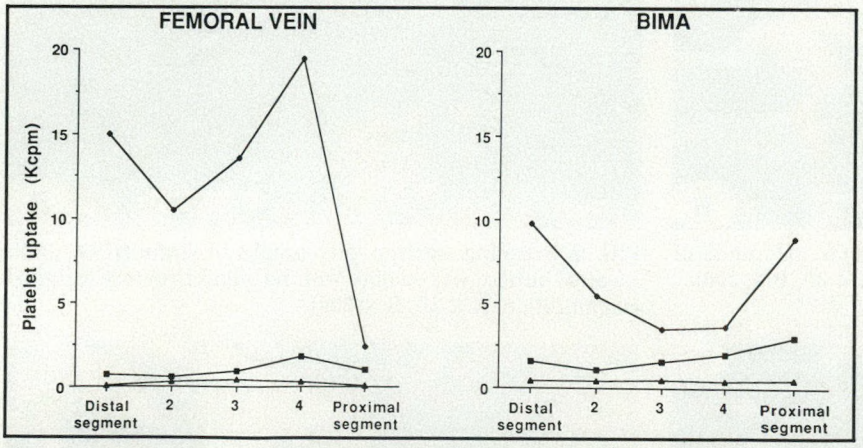

FIG. 3. Graphic representation of platelet uptake along graft segment of BIMA grafts and autologous femoral veins for short- (diamonds), medium- (squares) and long-term (triangles) implantations.

Table III. Platelet Uptake (Net cpm) by BIMA and Autologous Femoral Vein Grafts

Graft	Implantation group	Graft segment				
		Distal	2	3	4	Proximal
Femoral vein	Short term	15 202	10 552	13 200	18 953	2 540
	Medium term	892	588	920	1 885	1 300
	Long term	291	403	463	265	206
BIMA	Short term	9 845	4 966	3 343	3 621	8 488
	Medium term	1 501	1 240	1 542	1 724	2 993
	Long term	393	429	571	387	412

Discussion

Bovine heterografts have not evolved as outstanding blood conduits when used as primary vascular replacements.[22,23] Despite some enthusiastic reports,[24-26] there are widely recognized weaknesses.[7] Even the Solco prosthesis, an interesting model, did not meet clinical needs and was wisely abandoned after biodegradation became evident.[27] Caution is indicated before introducing any new chemically processed bovine heterograft and the following questions must be asked:

- Is the BIMA a valuable graft in terms of patency?
- How stable biologically is this chemically processed artery?

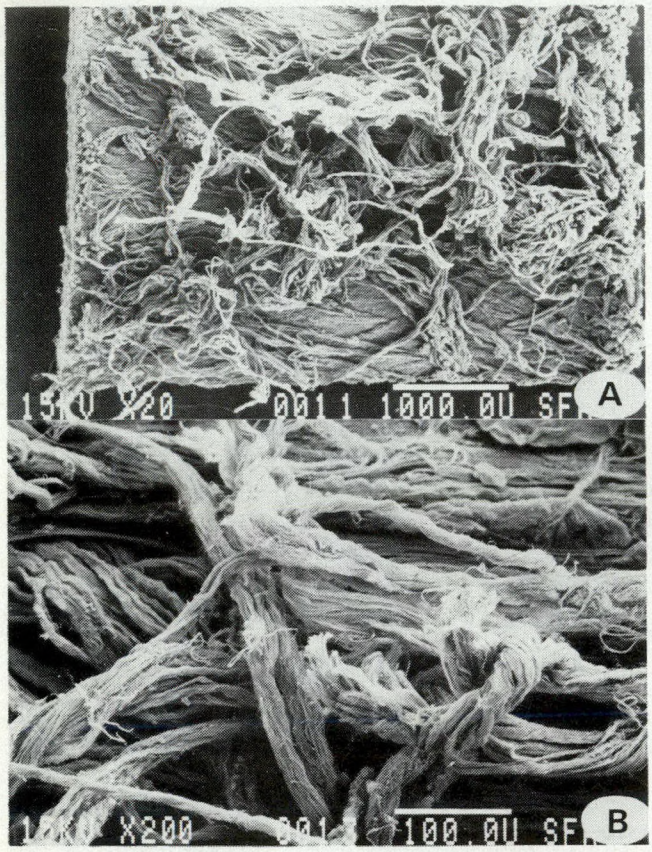

FIG. 4. Scanning electron micrographs of external tunica of virgin BIMA graft (original magnification, A × 20, B × 200).

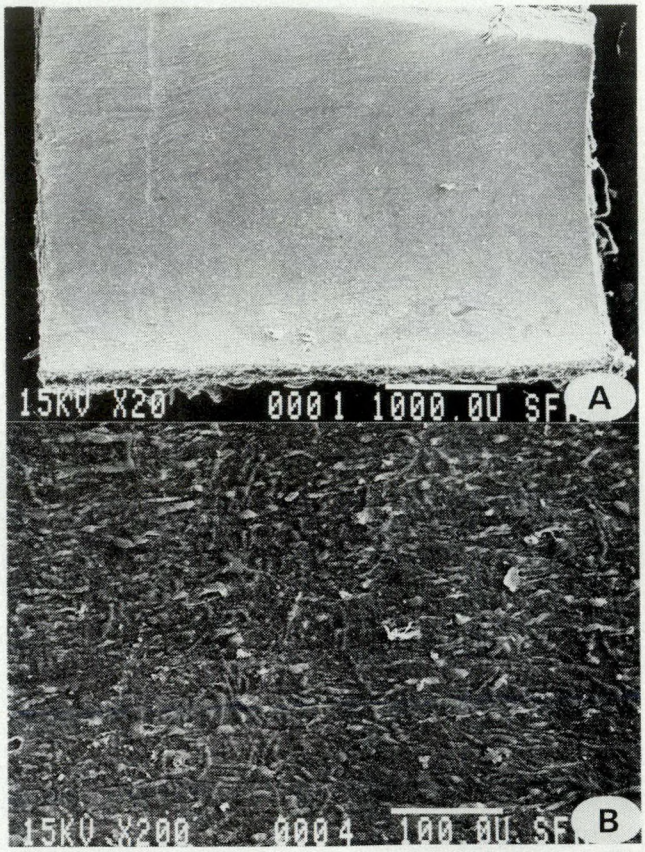

FIG. 5. Scanning electron micrographs of virgin BIMA graft. Luminal surface was smooth with no sign of rupture (original magnification, A × 20, B × 200).

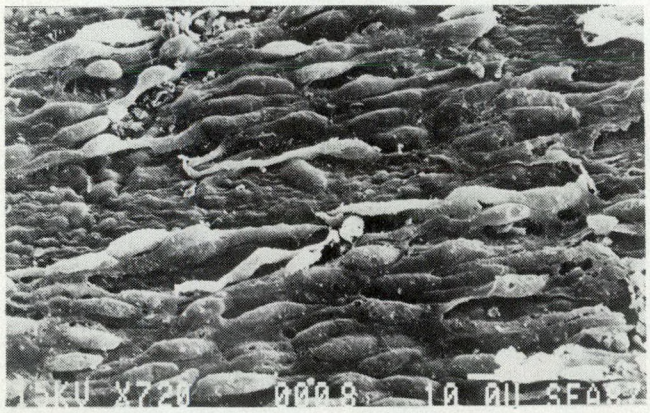

FIG. 6. Flow surface of BIMA graft is still covered with endothelial cells. However, because of processing, those cells are no longer viable (original magnification, × 720).

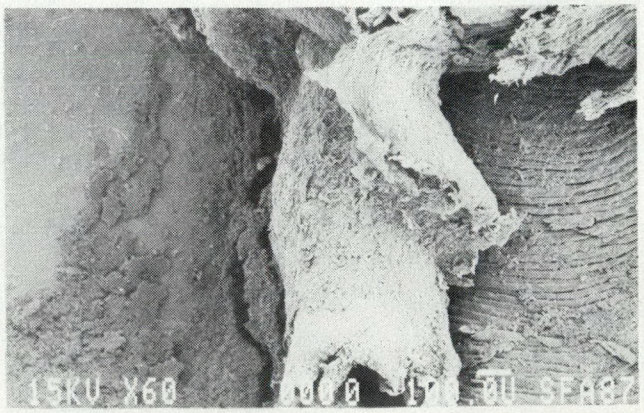

FIG. 7. Thrombus matrix is still present at anastomotic sites of BIMA graft 2 weeks after implantation (original magnification, × 60).

• What are the likely failure mechanisms?

Compared with autologous vein, the patency rates achieved with the BIMA are much lower,[28,29] which is not unexpected, since the vein is the gold standard of arterial substitutes.[30] Yet, the patency rates compare favourably with any synthetic blood conduit tested in our laboratories and the BIMA is second to homologous vein either fresh or frozen.[31-33] Moreover, fibrinogen and platelet retention are lower than that of alternative arterial substitutes. Healing is limited, however, to the development of a pannus over the anastomotic areas; the rest of the conduit should, therefore, present an antithrombogenic surface whose in-vivo properties should not be altered in order to maintain this blood compatibility.

The BIMA graft has demonstrated structural strength with preservation of the elastic network during processing. A mild fibrosis was present in the media soon after implantation. The usefulness of this graft lies in its capacity to preserve the smoothness of the flow surface, and on the development of an external fibrotic capsule. Quality control should be exacting to ensure that defect-free grafts are implanted. We are unconvinced that the currently accepted standards constitute a sufficient guarantee.[34] Additional testing, involving endoscopy[35] and measurement of the electrical impedance of the graft wall[36] should be mandatory. It is evident that handling should be atraumatic in order to maintain the integrity and antithrombogenic characteristics of the graft material.

Experiments to date do not permit researchers to predict the future failure mechanisms of the BIMA in humans; the dog remains a poor model for evaluating chemically processed grafts.[37] Usually, in dogs, the grafts develop fibrous hyperplasia, which rapidly becomes occlusive, and fail because of thrombosis. Administration of acetylsalicylic acid contributes to better patency

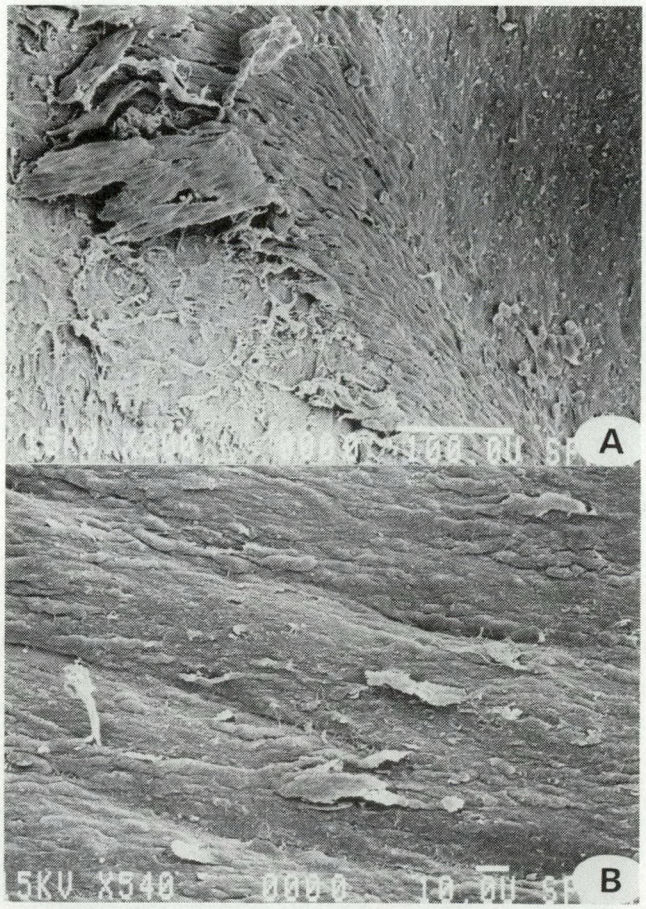

FIG. 8. Scanning electron micrographs of BIMA graft 1 month after implantation. Presence of endothelial cells along anastomosis is limited to pannus (A) (original magnification, × 200). Luminal surface remained smooth with some nonviable original cells (B) (original magnification, × 540).

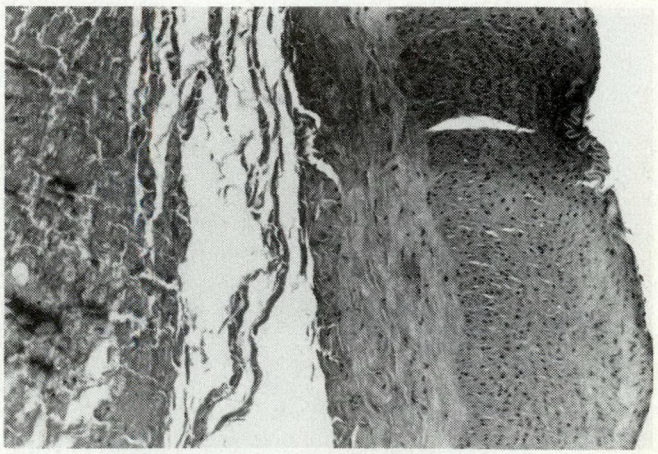

FIG. 9. Light microscopic view of BIMA prosthesis implanted for 3 months. Elastic lamina is no longer visible (original magnification, × 100).

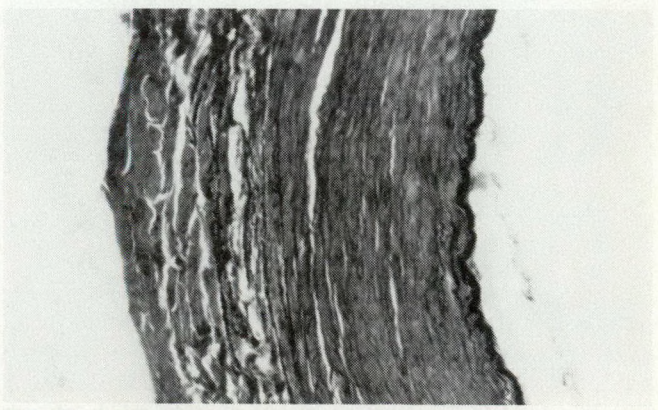

FIG. 10. Light microscopic view of BIMA prosthesis implanted for 6 months. Fibrosis is mild and elastic lamina is still visible (original magnification, × 100).

rates for chemically processed grafts.[38] In humans, with the absence of complete endothelialization of the flow surface, failure mechanisms are very different and probably related to lipid uptake. Lipids are retained on the luminal surface and then penetrate the wall and cannot be drained off because lymphatic vessels are absent. The collagen bundles become plasticized and stretched; they may rupture, leading to tissue resorption.[39] Dilatation is accompanied by additional cholesterol uptake and any bacteremia, however transient, may permit colonization of the glycocalyx biofilm.[40]

Because of its patency rates and firm structure, we believe that clinical trials using the BIMA graft can be undertaken for specific purposes in selected patients. Its use in aortocoronary bypass is not recommended since results remain inferior to the autologous vein graft because neo-endothelialization is absent, and this leads to an unfavourable prostacyclin-thromboxane balance. We would be reluctant to use the BIMA graft in peripheral vascular surgery where frequently associated lipid abnormalities and ulcers are likely to cause bacteremia. Thus, the recommended application for BIMA is as a secondary access for arteriovenous fistulas. Should the material prove highly successful, its use might be extended.

Conclusions

The new bovine internal mammary artery heterograft has some interesting features and is an acceptable blood conduit in terms of patency rates and structural stability. The luminal surface of the graft is blood compatible, and the deposition of a thrombotic matrix is limited to both anastomotic areas. However, autologous vein is still the material of choice for aortocoronary bypass and in peripheral vascular surgery. Although the dog is a poor model for evaluating the BIMA prosthesis, encouraging results should stimulate researchers to pursue clinical trials.

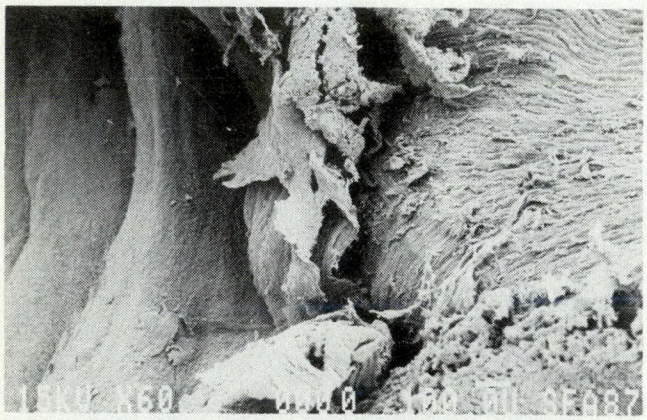

FIG. 11. Thrombus matrix is still present at anastomotic sites of autologous femoral vein 2 weeks after implantation (original magnification, × 60).

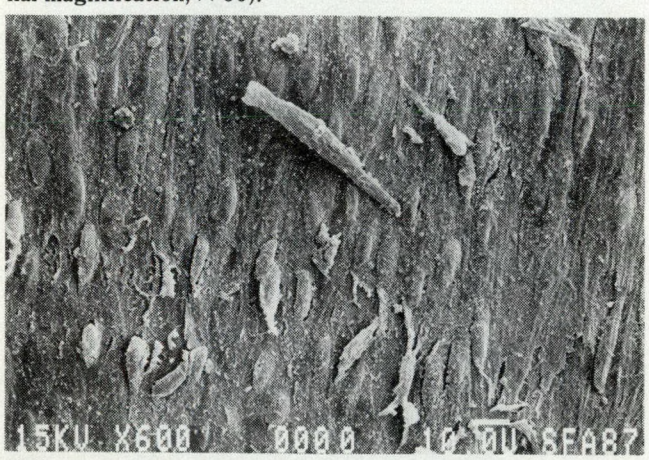

FIG. 12. Fragile development of veil of endothelial cells on luminal surface 3 months after implantation (original magnification, × 600).

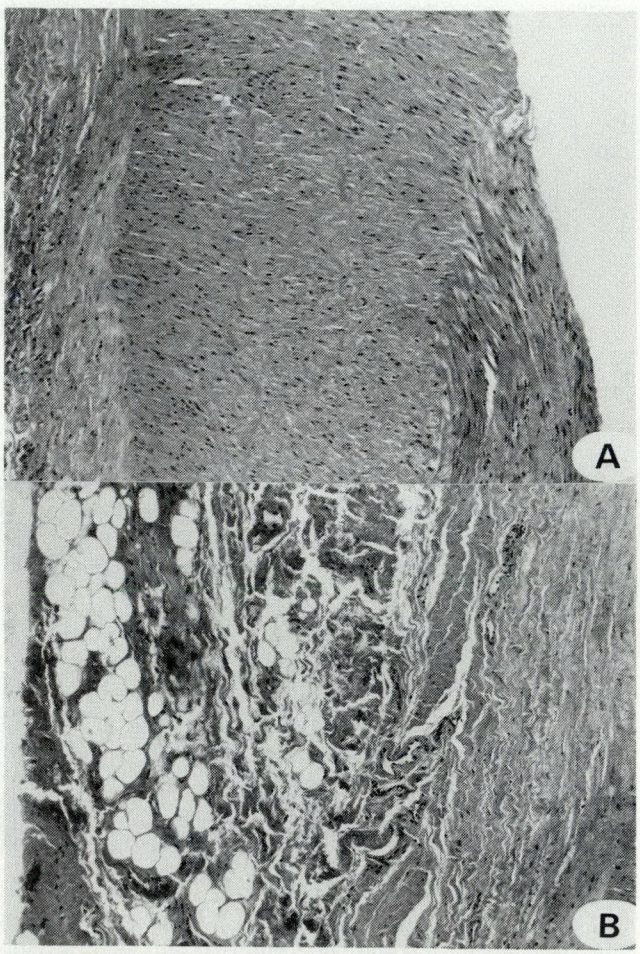

FIG. 13. Light microscopic views of femoral vein implanted for 3 months with important parietal fibrosis (A) and granulomatous reaction in adventitia (B) (original magnification, × 100).

We acknowledge the technical assistance of Pierre Casey, Marielle Corriveau, Karen Horth, Nicole Massicotte, Marcel Normandin and Jacques Rodrigue. We thank Drs. C. Gosselin, G. Roy, C. Poirier and J. Couture for their help and guidance.

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Effect of a Direct Current Field on Axons After Experimental Spinal Cord Injury

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There is evidence that direct current (DC) stimulation promotes neurologic recovery in spinal cord injury. The authors conducted a morphometric analysis of axons at the site of spinal cord injury in adult rats treated with a DC field. Ten rats received a 17-g and 15 rats a 53-g clip compression injury and were treated with either a sham (control) or a functioning DC stimulator for 8 weeks. Five normal rats were also assessed.

There was a significant relation ($p < 0.0001$) between the severity of injury and the number of axons at the injury site. After the 17-g injury, there was no significant difference in the number of axons between control and treated rats. However, after the 53-g injury, there were significantly ($p < 0.05$) more axons in treated than control rats. Both degrees of injury caused preferential destruction of large-calibre axons. Subsequent analysis showed that the axon diameter of treated rats with 17-g or 53-g injury was significantly greater ($p < 0.05$) than that of control rats with 17-g or 53-g injury. These data, for the first time, show that the application of a DC field increases the number and calibre of axons at the site of a spinal cord injury and enhances the survival or regrowth of axons following spinal cord injury in the rat.

Il existe des preuves que, dans les cas de lésion spinale, la stimulation à l'aide de courant direct (CD) favorise la guérison neurologique. Les auteurs ont mené une analyse morphométrique des axones au siège des lésions spinales, chez des rats adultes traités à l'aide d'un champ de CD. Les lésions ont été provoquées chez 10 rats par une compression de 17 g appliquée à l'aide d'une pince, et chez 15 autres rats par une compression de 53 g. Les animaux furent ensuite traités pendant 8 semaines soit par stimulation simulée (groupe témoin), soit par stimulation réelle à l'aide de CD. Cinq rats normaux furent aussi évalués.

On a constaté une relation significative ($p < 0.0001$) entre la gravité des lésions et le nombre d'axones au siège des lésions. Dans les cas de lésions de 17 g, aucune différence significative n'a été observée dans le nombre d'axones entre les animaux témoins et les animaux traités. Toutefois, après une lésion de 53 g, il y avait significativement plus d'axones ($p < 0.05$) chez les rats traités que chez les témoins. Quelle que soit leur gravité, les lésions causaient une destruction préférentielle des axones de gros calibres. L'analyse subséquente a révélé que le diamètre des axones des rats traités était significativement plus gros ($p < 0.05$) que celui des témoins, qu'il s'agisse de lésions de 17 g ou de 53 g. Pour la première fois, des résultats démontrent que l'application d'un champ de CD augmente le nombre et le calibre des axones au siège d'une lésion spinale et favorise la survie ou la regénération des axones après une lésion spinale chez le rat.

Direct current (DC) fields have been shown to enhance the proliferation of neurites in culture,[1,2] to promote axonal sprouting and decrease retrograde axonal degeneration[3–7] and to promote recovery[8,9] and regeneration[4,5] of injured spinal cord axons in mammals. In this study, we investigated the effect on axon counts and other morphometric parameters, including myelination index and axon diameter, of DC stimulation of axons at the site of cord injury, using a computer-assisted line-sampling technique. Our aim was to provide insight into the cellular effects and mechanisms of action of DC fields on injured spinal cord axons.

Methods

Experimental Procedures

A total of 30 rats were used in the study (25 with spinal cord injuries and 5 normal controls). Twenty-five adult rats underwent laminectomy at C7–T1 and were subjected to a 1-minute clip compression injury of the cord at C8. The rats were randomly allocated to one of two severities of cord injury by using a modified aneurysm clip to exert a force of either 17 g (10 rats) or 53 g (15 rats).[10] They were further blindly randomized to receive either DC stimulation (14 μA) or act as controls (0 μA) (Table I). The design, manufacture, electrical characteristics and method of implantation of the DC stimulators have been described elsewhere.[9]

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Briefly, immediately after cord injury, the electrodes, attached to the stimulator by insulated platinum wire, are placed epidurally with the anode proximal and the cathode distal to the injury site.

Postoperatively, clinical neurologic function was assessed each week by the inclined plane technique.[11] After 8 weeks, motor and somatosensory evoked potentials were recorded, and the axonal tracer, horseradish peroxidase (HRP), was introduced into the cord at T6. Coronal sections through the brain stem and motor cortex were examined, and the number of neurons, retrogradely labelled by HRP, were counted.

The injury site was sectioned transversely at 400 μm with a vibrotome, postfixed in a 2% osmium tetroxide/3% sodium ferrocyanide solution, immersed in 2% aqueous uranyl acetate and embedded in araldite plastic. The blocks were sectioned serially on an ultramicrotome for light and electron microscopy. A quantitative assessment of axons at the injury site was then performed. The spinal cord of five normal rats was similarly evaluated.

Line-Sampling Technique

Two independent, blinded observers (M.G.F. and T.H.W.) evaluated the spinal cord sections using the line-sampling technique of Blight.[12] The section with the most severe lesion from each rat, determined by inspection, was selected. A Zeiss photomicroscope attached to a camera lucida was used to measure the number, minor axis and myelin thickness of axons intercepted by 48 radial sample lines (drawn from the centre of the cord at even intervals of $2\pi/48$ radians) at 1000× magnification with the aid of a digitizing tablet interfaced to a microcomputer. Myelination index (MI) was calculated according to the following formula: $MI = a/a + 2m$, where a = minor axis and m = myelin thickness.[12] The estimated total number of axons within a section was derived using an algorithm based on line-sampling theory.[12]

To confirm the accuracy of the line-sampling technique, area counts were performed in the five normal rats. The total number of axons in a quadrant of the cord (the area bounded by 12 of the 48 radial sample lines) was compared with the total number of axons in the same sector estimated by line sampling.

Statistical Analysis

The data were analysed on the University of Toronto IBM 4381 mainframe computer using the Statistical Analysis Systems (SAS version 5.16) statistical programming language. Analysis of variance and linear regression were used to analyse continuous data. Later comparisons were made using Tukey's HSD test.[13] The results were expressed as mean ± SEM; differences were considered significant at $p < 0.05$.

Results

This study is part of a larger investigation on the effects of DC fields in experimental spinal cord injury. In it, we document the detailed quantitative analysis of axons at the injury site. Results of the inclined plane assessment, electrophysiologic recordings and axonal tracing studies have been reported elsewhere.[9] They showed that DC stimulation promoted clinical recovery of neurologic function, enhanced axonal function in the motor tracts of the cord and increased the number of HRP-labelled axons traversing the injury site.

The axonal morphometric data are summarized in Table I. The number of axons in the cord of normal rats was 458 000 ± 50 000. Spinal cord injury resulted in a significant ($p < 0.0001$) decrease in the number of axons at the injury site. Although there were no signficant differences in the number of axons between control and treated rats with 17-g injuries, for 53-g injuries the treated rats had significantly ($p < 0.05$) more axons at the injury site than controls. When we

Table I. Axon Morphometry (Mean ± SEM)*

Group	No. of rats	Axon counts	Axon diameter, μm	Myelination index†
Normal	5	458 000 ± 50 000 A	1.94 ± 0.07 A	0.62 ± 0.01 A
17-g injury				
Treatment	6	55 100 ± 23 200 B	1.46 ± 0.01 B	0.66 ± 0.01 B
Control	4	52 200 ± 23 200 B	1.31 ± 0.02 C	0.67 ± 0.01 C
53-g injury				
Treatment	7	51 700 ± 8 300 B	1.39 ± 0.01 D	0.67 ± 0.01 C
Control	8	25 300 ± 8 500 C	1.17 ± 0.02 E	0.72 ± 0.01 D

*Means with different letters beside each column are significantly different ($p < 0.05$) by analysis of variance and Tukey's HSD test.
† The ratio of axon diameter to fibre diameter. Data from axons smaller than 3 μm are excluded due to limited precision of the measurement apparatus.

examined the distribution of axons in the various cord funiculi, we found that there were significantly ($p < 0.05$) more axons in the ventral and ventrolateral funiculi of the cord in 53-g injury treated rats than in controls; in contrast, there were no differences between axon counts in the dorsal and dorsolateral funiculi between control and treated rats. The axon counts of control and treated rats with 17-g injuries were similar in all funiculi, although treated rats showed a 60% increase in axon counts in the ventrolateral funiculus (29 100 ± 11 100 versus 18 200 ± 9100, $p > 0.05$).

We noted a preferential destruction of large-calibre axons (Table I). For example, there was a significant difference ($p < 0.0001$) in the mean axon diameter between normal (1.94 ± 0.07 μm) and injured cord (1.35 ± 0.10 μm, pooled data). Furthermore, the mean axon diameters of 17- and 53-g treated rats were significantly greater than those of their respective controls (Table I).

Marked post-traumatic demyelination resulted from the spinal cord injury. It was reflected by a significant ($p < 0.05$) difference in the myelination index between axons in normal and injured cord (Table I). The demyelination was generally more severe in rats having 53-g injuries than in those with 17-g lesions. Furthermore, DC stimulation was associated with less demyelination in axons larger than 3 μm for both 17- and 53-g treated rats compared with their respective controls (Table I).

Axon counts derived using 48 sample lines showed an excellent correlation with the total counts of a cord quadrant. For example, the counts based on line sampling and the total counts differed by approximately ± 5% ($t = 1.21$, $p > 0.05$), confirming the validity and robustness of the line-sampling technique.

Discussion

This study is the first to evaluate quantitatively the effect of an applied DC field on axon counts and other morphometric parameters after spinal cord injury in a mammal. The data show that the DC field is associated with an increased number of surviving myelinated axons at the injury site, particularly large-calibre axons, and that it decreases the extent of post-traumatic demyelination.

The data are consistent with our previous demonstration[9] that DC stimulation of the injured mammalian cord results in an increased number of axons, retrogradely labelled by HRP, which traverse the site of cord injury. Furthermore, the effects on axon number, diameter and myelination index provide a structural basis for the clinical neurologic and electrophysiologic effects of DC fields on cord injured rats.[8,9]

Although it is unclear why axon counts were not increased in treated rats with 17-g injuries, the results are consistent with our previous finding of a lack of clinical, electrophysiologic or anatomical improvement at this severity of injury. It is possible that the failure to detect a difference in axon counts in the 17-g injury group may represent an artifact of the relatively small sample size ($n = 10$). For example, treated rats with 17-g injuries, when compared with controls, had a 60% increase in the number of axons in the ventrolateral funiculus. A post hoc calculation of sample size[13] affirmed that this difference would have achieved statistical significance had the sample size been approximately doubled. In future studies, it may prove fruitful to re-examine whether DC fields can effect functional and anatomical recovery in mild or moderate spinal cord injuries.

Spinal cord injury resulted in a preferential loss of large-calibre axons, similar to the findings of Blight[12] and Blight and Decrescito,[14] who suggested that axonal shearing may be a major mechanism of axonal injury after cord compression. The modulus of rigidity, defined as the amount of stress required to produce a unit of shear, varies inversely as the fourth power of the radius of a cylinder,[15] and may explain the selective loss of large axons which would be more vulnerable to shear forces. We showed that the applied DC stimulation enhanced the survival of large-calibre axons in treated rats with both 17-g and 53-g injuries. It is possible that DC stimulation equally enhances the survival of all axons, regardless of size, but because cord injury results in the preferential loss of large-calibre axons, the stimulation effect is most apparent in large spinal cord axons.

Although the mechanism of action of DC fields on injured axons is incompletely understood, there is evidence that modulation of transcellular ionic fluxes may be involved. For example, around severed axons there exists an extracellular field which is associated with a strong inward "injury current", due mainly to Na^+ and Ca^{++} ions.[16] It has been proposed[6] that the distal placement of the cathode of an applied electrical field should drive this "injury current" in the opposite direction. Since Ca^{++} is known to disrupt neurofilaments and to promote axonal degeneration,[17] one major effect of applied DC fields might be to reduce retrograde axonal degeneration, which in turn might facilitate recovery and regeneration. We are studying this hypothesis.

In conclusion, in this investiga-

tion we have demonstrated that DC fields promote the survival of myelinated spinal cord axons and reduce the extent of demyelination following experimental spinal cord injury.

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Nonoperative Management of Complications of Percutaneous Renal Nephrostomy

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Between 1984 and 1986 at the Wellesley Hospital in Toronto, 210 percutaneous renal nephrostomies were performed for drainage and 140 were done to provide access for nephrolithotomy. Less than 2% of the patients experienced complications requiring intervention and less than 0.5% required an open surgical approach for the management of procedure-related problems. Complications that were managed conservatively included splenic puncture, false aneurysm, laceration of the renal artery, arteriovenous fistula, hemorrhage requiring transfusion, pneumothorax-empyema, urinoma, septic shock and the hemolysis-hyponatremia-renal shutdown syndrome.

Entre 1984 et 1986, 210 néphrostomies rénales percutanées ont été pratiquées pour fins de drainage à l'Hôpital Wellesley de Toronto, et 140 autres ont été effectuées pour offrir une voie d'accès pour une néphrolithotomie. Moins de 2% des patients ont souffert de complications nécessitant une intervention chirurgicale et moins de 0.5% ont nécessité un abord chirurgical ouvert pour corriger un problème causé par l'intervention. Parmi les complications traitées de façon conservatrice, on compte: perforation splénique, faux anévrisme, lacération de l'artère rénale, fistule artério-veineuse, hémorragie nécessitant une transfusion, empyème de pneumothorax, urinome, choc septique et le syndrome hémolytique, hyponatrémique et oligo-anurique.

Over the past decade, percutaneous nephrostomy has emerged as the primary therapeutic approach for retained renal calculi. In combination with extracorporeal shock-wave lithotripsy, percutaneous nephrolithotomy has virtually eliminated the need for an open procedure. Likewise, the need for an open approach to obstruction at the ureteropelvic junction has been markedly reduced by using percutaneous pyeloplasty (endopyelotomy). Whether access is obtained under fluoroscopic or ultrasonic guidance, morbidity, mortality and convalescence time are decreased compared with an open surgical procedure.

Patients and Methods

Between January 1984 and December 1985, 350 percutaneous renal nephrostomies were performed for drainage (210) or nephrolithotomy (140). Patients ranged in age from 21 to 81 years, with a 2:1 male predominance. Duration of hospital stay ranged from 3 to 28 days (mean 11 days).

Renal access was achieved in all cases under fluoroscopic guidance. Retrograde placement of a ureteric occlusion balloon catheter for injection of contrast medium, or as an aid to dilation of the renal system, preceded percutaneous puncture in most nephrolithotomy cases. All procedures were performed using

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local anesthetic, supplemented by analgesics administered intravenously. The following five brief case reports illustrate the problems encountered and their management.

Case Reports

Case 1

One patient suffered laceration of the right renal artery. This was managed by temporary balloon occlusion of the main renal artery (Figs. 1 and 2), after which the percutaneous tract was embolized with Gelfoam (Fig. 3). On release of the occlusion balloon, after 8 minutes, the hemorrhage had ceased and normal perfusion was noted through the main renal artery.

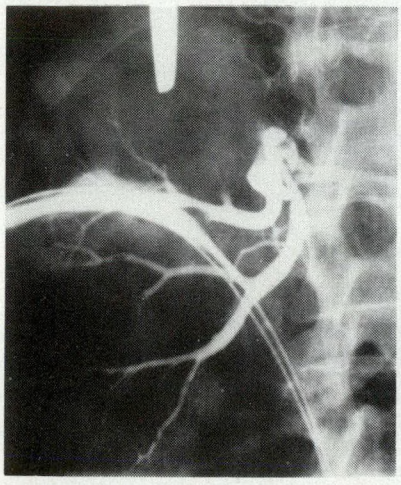

FIG. 1. Case 1. Balloon tamponade of renal artery laceration before application of Gelfoam.

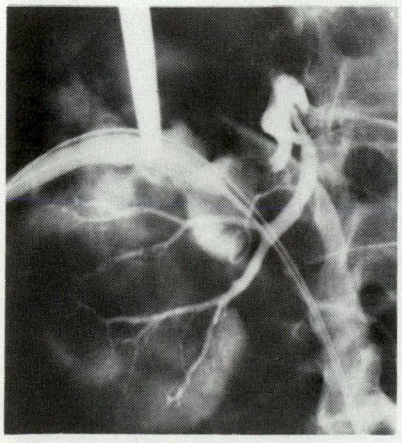

FIG. 2. Case 1. Massive extravasation. Balloon catheter is in place.

Case 2

A renal artery pseudoaneurysm (Fig. 4) formed after a percutaneous access procedure. It was successfully managed nonoperatively by selective cannulation of the involved vascular branch and by embolization with autologous clot and Gianturco coils.

Case 3

One patient suffered perforation of the upper ureter complicated by an obstructive clot in the lower ureter. This resulted in the formation of a massive urinoma. Nephrostomy drainage was by placement of a ureteric stent from above, parenteral administration of antibiotics and intravenous administration of furosemide. The urinoma resolved completely within 24 hours.

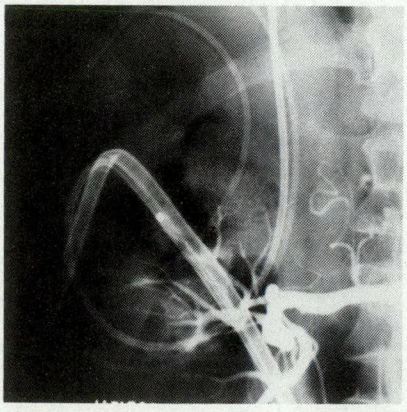

FIG. 3. Case 1. Bleeding tamponaded with Gelfoam.

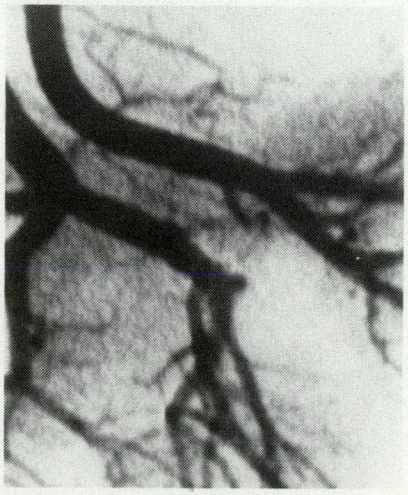

FIG. 4. Case 2. False aneurysm in branch of renal artery.

Case 4

During attempted placement of a left internal ureteric stent this patient suffered laceration of the spleen (Fig. 5). After receiving blood transfusion the patient remained hemodynamically stable and was discharged 14 days later. There were no late sequelae.

Case 5

After routine dilatation of a percutaneous tract, established for nephrolithotomy, the balloon could not be deflated. A second percutaneous nephrostomy provided access to the balloon which was punctured, permitting the entrapped dilator to be removed.

Results

Complications requiring active intervention occurred in less than 2% of the 350 patients; they included hemorrhage requiring transfusion (8), pneumothorax-empyema (2),

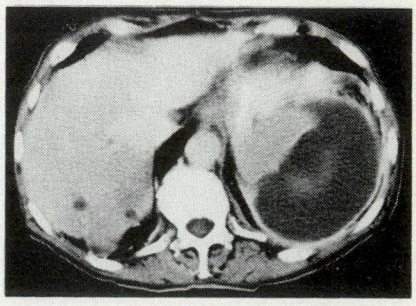

FIG. 5. Case 4. Splenic perforation.

"CIPRO®
Ciprofloxacin Hydrochloride
THERAPEUTIC CLASSIFICATION
Antibacterial Agent

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.

nephrostomy dislodgement (1), failure of a dilated balloon catheter to deflate (1), formation of a urinoma (1), retroperitoneal hematoma (1), pleural effusion (2), delayed hemorrhage (3), splenic laceration (1), renal artery pseudoaneurysm (1), renal artery laceration (1) and septic shock (10).

Discussion

Since percutaneous renal access has become a routine urologic procedure, the incidence of related complications has increased. Those reported include bleeding requiring transfusion, infection, urinoma, pelvic laceration, ureteral avulsion, obstruction at the ureteropelvic junction or ureteral stricture, pneumothorax or hemothorax, bowel injury, renal vein thrombosis, arteriovenous fistula formation, renal or perirenal abscess, and death secondary to myocardial infarction, sepsis or respiratory failure.[1-7] Most of these complications can be managed conservatively[1-6] as we have illustrated.

With improved angiographic expertise, vascular complications such as pseudoaneurysm, laceration of a branch of the renal artery and arteriovenous fistulas can be managed by techniques of vascular access and embolization.[4,6] Case 1, in which Gelfoam embolization in the percutaneous tract was used, is a recent variation of previous techniques.[4,6]

Advances in intensive care medicine have permitted successful management of septic shock and hemolysis-hyponatremia-renal shutdown syndrome, conditions that are potentially fatal. Increasing expertise has resulted in percutaneous nephrolithotomy and extracorporeal shock-wave lithotripsy virtually replacing open surgical lithotomy and permits nonoperative management of associated complications.

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Natural History of Vertical Abdominal Parietal Closure: Prolene Versus Dexon

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The long-term outcome of laparotomy incisions after mass closure (taking large tissue bites through all layers) with continuous polypropylene (Prolene) in 95 patients or interrupted polyglycolic acid (Dexon) sutures in 105 patients was compared by randomized prospective study. Of the 200 patients, 194 incisions were median and 2 were paramedian (4 patients were excluded). There was one wound dehiscence (0.51%) due to slippage of a polypropylene knot. At 5-year follow-up, 4 hernias were found in incisions repaired with polypropylene, compared with 11 in the polyglycolic acid group; 10 of the 11 occurred after the first year ($p = 0.01$). Wound infections were slightly more frequent in patients whose incision was closed with polypropylene. Only two hernias in each group occurred in patients who had had wound infections. Polypropylene and polyglycolic acid both allow rapid and secure closure of vertical laparotomy incisions, but late herniation is more common when polyglycolic acid sutures are used.

Dans une étude prospective et randomisée, on a comparé l'évolution à long terme des incisions de laparotomie, soit après fermeture large chez 95 patients (en prenant de larges piqûres à travers toutes les couches de tissus) à l'aide de polypropylène continu (Prolene), soit après suture à points séparés chez 105 patients à l'aide de fil d'acide polyglycolique (Dexon). Chez ces 200 patients, on a compté 194 incisions médianes et 2 paramédianes (4 cas ayant été éliminés). On a enregistré une seule désunion de suture de plaie (0.51%) due au lâchage d'un noeud de polypropylène. Après 5 ans de surveillance des suites thérapeutiques, on a dénombré 4 hernies d'incisions réparées avec du polypropylène, comparativement à 11 dans le groupe acide polyglycolique; 10 des 11 sont survenues après la première année ($p = 0.01$). Les infections de plaie ont été légèrement plus fréquentes chez les patients dont l'incision avait été refermée avec le polypropylène. Seulement deux hernies dans chaque groupe ont été notées chez des patients qui avaient subi des infections de plaie. Le polypropylène et l'acide polyglycolique assurent, tous deux, une fermeture rapide et solide des incisions verticales de laparotomie, mais les hernies tardives sont plus fréquentes avec les sutures d'acide polyglycolique.

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Although the incidence of wound dehiscence has decreased to nearly 1% with the use of mass closure (through and through, taking large tissue bites) and proper surgical technique,[1–4] wound failure because of incisional hernia remains a problem.[5] In addition to a 5% to 7% incidence of herniation in the first year after laparotomy,[1] just as many hernias appear again later,[6–8] and the results of repair by conventional methods are still poor.[9,10]

The main causes of herniation are wound dehiscence[11] and postoperative complications, such as wound infection, pulmonary complications and abdominal distension.[1,12] The role played by the type of suture material in causing postoperative herniation is uncertain. Many studies[13–17] have shown no difference in the incidence of herniation with either absorbable or nonabsorbable sutures, but the follow-up has been short. Others[18,19] have noted more hernias when absorbable sutures were used.

We conducted a prospective randomized study of patients who had mass closure of vertical laparotomy wounds to identify and compare the outcomes of incisions closed with absorbable and nonabsorbable sutures.

Patients and Methods

Two hundred consecutive vertical laparotomy wounds longer than 10

cm were randomized at operation by the last digit of the patient's year of birth. Patients born in even years had the wound closed with interrupted Smead–Jones sutures[20] of no. 1 polyglycolic acid (Dexon; Davis and Geck, Markham, Ont.), and patients born in odd years had the wound closed with continuous simple sutures of no. 1 polypropylene (Prolene; Ethicon Ltd., Peterborough, Ont.). In each case, care was taken to include musculoaponeurotic tissue bites at least 1 cm from the wound edge. Sutures were not pulled tight and they were placed 1 to 2 cm apart. The subcutaneous fat was approximated with interrupted sutures of 4-0 polyglycolic acid and the skin with simple sutures of 5-0 nylon (Ethilon; Ethicon Ltd.).

For each patient, the age, sex, weight and height and preoperative blood concentrations of hemoglobin, urea nitrogen and bilirubin were recorded. Values of ideal body weight for height and body build were obtained from standard tables,[21] and the percentage actual of ideal body weight was derived for each patient. The operative diagnosis, type of operation, degree of wound contamination,[22] presence of a previous abdominal wound, urgency of operation and perioperative use of antibiotic prophylaxis and steroids were noted. For some patients, we measured the time taken to close the fascia and the length of the wound.

After operation, the patients were followed up daily by physiotherapy personnel for development of pulmonary complications. Sputum culture and chest x-ray films were obtained as indicated clinically. A scoring system was used to evaluate postoperative pulmonary complications, four or more points being regarded as significant.[23] The wounds were inspected by infection control personnel 5 days after operation and before the patient was discharged. A further follow-up was made 1 month later.

A wound infection was diagnosed when pus drained from the wound.[24] A sample of the draining material was cultured. Wounds that were erythematous or tender were monitored until they drained pus or the signs subsided. The surgeon evaluated clinically any gross abdominal distension caused by urinary bladder, bowel or ascites during the first week postoperatively.

After discharge from hospital, the patients were followed up by a single surgeon at 1, 3, 6, 12, 24 and 60 months. The end-points for wound failure were wound dehiscence, diagnosed only when evisceration occurred, and incisional hernia, defined as a defect with sharp fascial margins and presenting as a bulge when the patient strained while standing. The outcomes with respect to these end-points were analysed by the life-table method.[25,26]

Statistical analysis was performed when necessary by Student's *t*-test, Fisher's exact test and χ^2 analysis with the Yates modification, and the outcomes derived from life-table data were compared by the log rank χ^2 equivalent.

Table I. Patient Data

	Dexon (n = 103)	Prolene (n = 93)
Mean age, yr (± SEM)	56.8 ± 17	55.8 ± 18
Sex (male/female), no.	44/59	48/45
Weight, actual/ideal, %	111.5 ± 20	111.6 ± 24
Hemoglobin (< 100 g/L), no.	8	13
Blood urea nitrogen (> 10.7 mmol/L urea), no.	10	5
Bilirubin (> 34.2 μmol/L), no.	6	6
Malignant disease, no.	29	21
Steroid use, no.	6	4
Primary/repeat incisions, no.	80/23	73/20

Results

Of the 200 patients who entered the study, 105 had fascial closure of the laparotomy wound with Dexon and 95 with Prolene. Two patients from each treatment group were excluded from further analysis. Two died within a week of surgery, a third required reoperation on the first postoperative day and in the fourth the protocol was violated by the use of retention sutures in addition to fascial closure. Thus, 196 incisions were evaluated; 194 were median and 2 paramedian. Fifty-two incisions were confined to the lower abdomen. In a few patients in each group, the incision was made through a previous laparotomy scar. Table I compares the treatment groups and shows that they were similar in mean age, sex distribution and patient weight, and in the frequency of anemia, jaundice, uremia, malignant disease and preoperative steroid usage.

Wound infections were slightly more frequent in incisions closed with Prolene, which was used more for emergency operations, than in incisions closed with Dexon, but the difference was not significant. Prophylactic use of antibiotics and wound class were also similar in the two groups (Table II). Table III shows the frequency of wound infection and type of operation performed in each treatment group.

Respiratory complications developed in 26 wounds closed with Prolene and in 21 closed with Dexon. Abdominal distension was recorded postoperatively in 33 pa-

tients in the Prolene group and in 27 in the Dexon group (not significant). Fascial closure time was 49 s/cm for Dexon and 41 s/cm for Prolene ($p < 0.05$).

The only case of wound dehiscence was caused by slipping of a Prolene knot. Incisional hernias were more frequent in the Dexon group, and the majority were seen after the first year of follow-up (Table IV). In each group, only two hernias developed in patients who had had wound infections. In Fig. 1, the outcomes in the two treatment groups are evaluated by the life-table method ($p < 0.05$).

Discussion

The ideal suture for fascial closure should not cause infection or irritation; it should achieve its purpose in holding the wound edges together but disappear when its work is done.[27] This implies that an absorbable suture should be ideal. However, studies have shown that when catgut, the natural absorbable suture, is used to close median and standard paramedian laparotomy wounds, the incidence of wound dehiscence is unacceptably high.[3] The reason is that catgut loses its tensile strength after only 10 days, well before healing fascia has gained sufficient strength. This is not a problem when modern synthetic sutures are used. Synthetic nonabsorbable sutures and absorbable sutures have markedly decreased the incidence of wound dehiscence, particularly when the technique of mass closure is applied.[20] In addition, Jenkins[2] and others,[16,17,28] have shown that for mass closure a continuous suture is as effective as interrupted sutures in preventing wound dehiscence, and can be placed more quickly. The present study, then, is an ethical and valid comparison of mass closure comparing polypropylene with polyglycolic acid sutures.

In our trial, the rate of wound dehiscence was 0.51%. Thus, we have confirmed that mass closure using either of these suture materials effectively prevents abdominal wound dehiscence. In mass closure, large tissue bites avoid the zone of increased collagenase activity that extends up to 5 mm from the wound margin,[29] and, compared with small bites, they distribute the tension in the suture over a large area, making tissue necrosis less likely.[4,30] As in previous studies,[16,17] continuous suture closure in our trial was completed more quickly than closure with interrupted sutures.

We have also shown that Dexon sutures are associated with more late herniations through laparotomy incisions than Prolene. This preponderance of late herniation in the polyglycolic acid group was not due specifically to postoperative complications, for only two hernias in each group developed after wound infections; also, pulmonary complications and abdominal distension were less frequent in the Dexon group than the Prolene group.

It seems likely that most hernias were caused by failure of the polyglycolic acid suture material. Aponeurotic incisions of the abdominal wall are much less vascular and heal more slowly than skin wounds. They require about 120 days to regain strength.[31] Unfortunately, polyglycolic acid loses 80% of its tensile strength within 2 weeks of operation,[32] and more than 90% within 3 weeks.[33,34] At that time, aponeurotic wounds have reached only 20% of the preoperative strength of the fascia. It is assumed that the tensile strength of polyglycolic acid is sufficient to prevent wound dehiscence, but that the suture fails during the collagen maturation phase of wound healing.[35] The resulting weakness presents later as an incisional hernia. Playforth and colleagues,[36] found that 1 month after operation radiopaque markers placed on the fascial margins at surgery showed a separation of more than 10 mm, predicting

Table II. Comparison of Factors Relating to Wound Sepsis

	Dexon	Prolene
Wound infection	11	19
Emergency/elective laparotomy	21/82	30/63
Prophylactic use of antibiotics	67	64
Wound class		
Clean	31	26
Clean-contaminated	53	51
Contaminated	19	16

Table III. Wound Sepsis by Type of Operation

Type of operation	Dexon		Prolene	
	Infected	Uninfected	Infected	Uninfected
Biliary	8	40	4	31
Upper gastrointestinal	2	21	8	30
Colorectal	1	29	5	19
Vascular	0	7	0	7
Miscellaneous	0	6	2	6

Table IV. Sequelae of Laparotomy by Group

Sequela	Dexon	Prolene
Wound infection	11	19
Wound dehiscence	0	1
Incisional hernia	11	4
Early	1	2
Late	10	2

$p = 0.01$

incisional herniation that may not be clinically apparent until more than 1 year after operation.

What, then, can be done to prevent postoperative incisional herniation? It remains to be seen whether more durable absorbable sutures such as polydioxanone (PDS; Ethicon),[37] or polyglactin 910 (Vicryl; Ethicon) will be more effective than polyglycolic acid in preventing late herniation. But it seems unlikely that they will, because Leese and Ellis[38] found that 20% of laparotomy wounds closed with PDS sutures developed incisional hernias compared with 8.5% closed with nylon. Moreover, of seven incisional hernias found by Wasiljew Winchester[39] during a mean month follow-up of 244 patients whose laparotomy wounds closed with continuous mature of polyglactin 910, or e followed a wound infectio alternative course is to accept the thesis of Douglas[31] that all aponeurotic wounds are potential sites of herniation. If this is so, delayed herniation can only be prevented by repair with nonabsorbable sutures, or by operating through muscle-sparing incisions in which intact muscle helps to buttress the repair.[40,41]

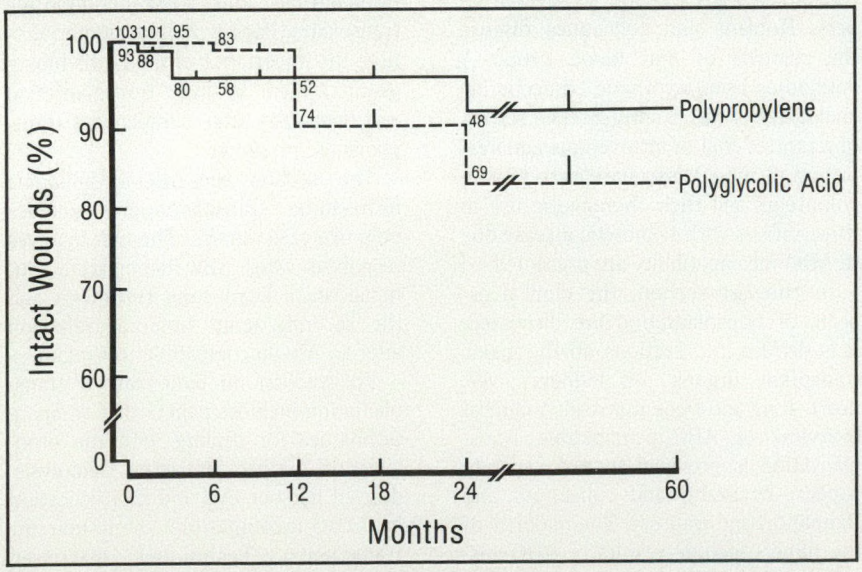

FIG. 1. Outcome in incisions closed with polypropylene (Prolene) and polyglycolic acid (Dexon). Vertical bars represent standard error of mean for interval.

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BOOK REVIEWS

ABO INCOMPATIBILITY AND TRANSPLANTATION. Edited by Aaron D. Bannett, Hans Brynger, Bo Samuelsson, Robert F. McAlack and Michael Breimer. 246 pp. Illust. Grune & Stratton, Inc., Philadelphia; W.B. Saunders Company Canada Limited, Toronto, Ont., 1988. $81.95. ISBN 0-8089-1951-2.

ABO-incompatible transplantation is becoming an important issue as the limitations of our pool of donor organs are reached. This book is a *Transplantation Proceedings* reprint from December 1987. It includes papers from the combined proceedings of the First International Symposia on ABO Incompatibility and Transplantation (Philadelphia, March 1987 and Gothenburg, Sweden, June 1987).

The book is divided into three sections. The first, on the basic science of the ABH system, emphasizes new developments in solving its underlying complexity. Papers on the current understanding of ABH antigen structure and tissue distribution are presented. In their paper, Socha and colleagues discuss the analogous animal blood-group systems and their place on the evolutionary scale.

The next section is on experimental transplantation. Because the ABO-incompatible transplant represents a model for acute humoral rejection, many of the papers are on xenografting. Indeed, many of the techniques presented for removal of pre-formed natural antibodies are applicable to the ABO-incompatible transplant. Cerilli presents an interesting paper on the importance of vascular endothelial antigen matching in kidney allografts, based on monocyte cross-matching. Paul's review of humoral rejection mechanisms is excellent. In several papers, Romano and colleagues discuss the removal of anti blood group A antibodies using synthetic trisaccharide analogues of the A antigen. The results of a limited trial of intravenous administration of these trisaccharides to human volunteers and their therapeutic use in three infants with hemolytic disease due to ABO incompatibility are presented.

In the last section, the clinical aspects of transplantation are discussed. It is divided into sections on the major transplant organs — kidney, liver, heart–lung and bone marrow. A clinical overview of ABO-incompatible transplantation is provided in two separate papers, by Starzl and colleagues and Rappaport and Dausset. The majority of the papers include results of ABO-mismatched kidney allografts, with particular emphasis on the A_2 to O graft. Different techniques for dealing with the anti blood group antibodies are put forward, including the use of immunoadsorbent columns produced by Chembiomed in Edmonton. Finally, the importance of Lewis blood-group matching in kidney allografts is reviewed in two articles presenting opposite viewpoints.

The section on liver transplantation deals primarily with survival following ABO-identical, ABO-compatible but nonidentical and ABO-incompatible transplants. Papers on hyperacute rejection, the importance of the Lewis blood-group system in liver transplantation and hemolysis after nonidentical transplants are presented.

The section on ABO-incompatible heart–lung transplantation includes only two case reports. The first involves hemolysis after ABO-incompatible but nonidentical heart–lung transplant and the second, acute humoral rejection after an ABO-incompatible transplant.

The section on bone-marrow transplantation includes papers that compare techniques for dealing with the problems of delayed or acute hemolysis, delayed hemopoiesis and graft rejection in ABO-incompatible bone-marrow transplants. Techniques discussed

continued on page 206

Ketoconazole in the Treatment of Osteomyelitis Due to *Candida albicans*

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Osteomyelitis caused by *Candida albicans* is a rare condition. The authors report its occurrence as an infective complication in the fractured phalanx of a 3-year-old boy. The infection was first thought to be due to *Staphylococcus aureus*, but a course of cloxacillin was unsuccessful, and when cultures of the injured finger grew *C. albicans*, a 3-month course of ketoconazole orally was begun. Ketoconazole was prescribed because, unlike amphotericin B, the antibiotic usually used in such cases, it is not nephrotoxic, it can be taken orally and it has proved successful in other reported cases of osteomyelitis due to *C. albicans*. The boy's infection resolved and fracture healing was confirmed radiologically.

L'ostéomyélite à *Candida albicans* est une affection rare. Les auteurs en décrivent un cas qui est survenu comme complication infectieuse de la fracture d'une phalange chez un garçon de 3 ans. Au début, l'infection fut attribuée à *Staphylococcus aureus*, mais un traitement à la cloxacilline s'avéra inefficace. Quand les cultures du doigt blessé mirent en évidence le *C. albicans*, une thérapie de 3 mois au kétoconazole par voie orale fut mise en route. On a prescrit le kétoconazole parce que, contrairement à l'amphotéricine B qui est habituellement employée dans ces cas, cet antibiotique n'est pas néphrotoxique et il peut être pris par voie orale. De plus, il s'est déjà montré efficace dans d'autres cas d'ostéomyélite à *C. albicans*. L'infection du garçonnet disparut et la radiographie vint confirmer la guérison de la fracture.

Osteomyelitis caused by *Candida albicans* is rare, and its optimal treatment is unknown. The toxicity of amphotericin B and the development of resistance to 5-fluorocytosine limit the use of these customary antifungal agents. We report a case of osteomyelitis due to *C. albicans* affecting the middle phalanx of an index finger; it was successfully treated with a 3-month course of ketoconazole taken orally.

Case Report

A 3-year-old boy sustained a cut to his left index finger at play. Within a week the digit became red and swollen. An x-ray film was made and amoxicillin was prescribed. The laceration healed over the next 7 days but the swelling and redness remained. Review of the x-ray film revealed a transverse fracture of the distal shaft of the middle phalanx of the injured finger, with a suggestion of superimposed infection (Fig. 1). The boy was admitted to hospital and started on an empirical 1-week course of cloxacillin (200 mg/kg daily intravenously, given every 6 hours) for infection assumed to be caused by *Staphyloccus aureus*. There was no evident improvement, so exploratory surgery with open débridement was performed. No pus was found. Easy mobility of the fracture indicated lack of healing. A deep swab and two curettage specimens were taken from the fracture site. Cefotaxime (100 mg/kg daily given every 6 hours) was administered intravenously for several days. When the culture results from the operative specimens all indicated *C. albicans* a 3-month course of keto-

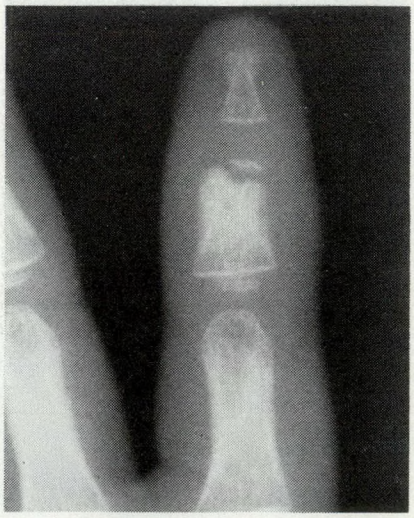

FIG. 1. Infected fracture of distal shaft of middle phalanx of left index finger.

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conazole taken orally (50 mg/d in a single dose) was begun. During this period, progressive healing was observed both clinically and radiologically (Fig. 2). No serious side effects of the drug were encountered, and the infection did not recur on 2-year follow-up.

Antifungal susceptibility tests showed that the *Candida* isolate was resistant to ketoconazole, but we decided to persist with the therapy in view of the boy's early clinical improvement.

Discussion

A recent review[1] uncovered only 58 cases of osteomyelitis due to *C. albicans* in the English literature. Our case, which meets the diagnostic criteria of Edwards and colleagues[2] — radiologic evidence of osteomyelitis plus isolation of *C. albicans* from deep tissue — was unusual in several respects. First, the infection involved a digit, whereas *C. albicans* usually affects single long bones, contiguous vertebral bodies or the sternum. Second, the infection appeared to be primary, following trauma, rather than secondary to bloodstream involvement or a surgical procedure. Finally, we used ketoconazole in place of the more widely favoured amphotericin B.

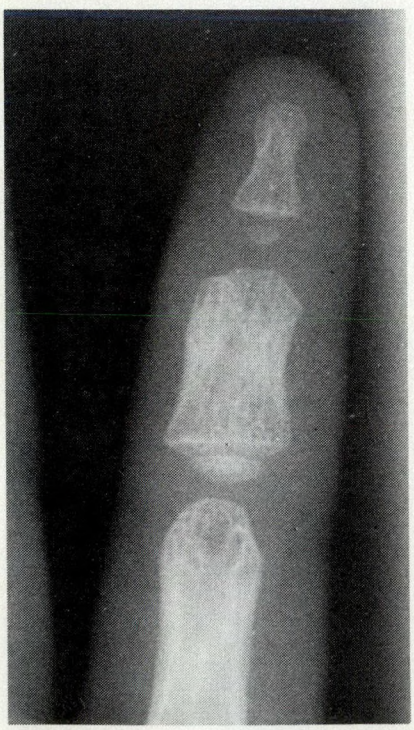

FIG. 2. Healing of lesion of middle phalanx.

This decision was based on the success of ketoconazole in blastomycosis,[3] another yeast-like fungal infection in which bone involvement is a prominent part. The relative resistance of our patient's isolate did not deter us from persisting with the drug, since previous investigators[4,5] have noted a poor correlation between its in-vitro activity and clinical performance. In addition, ketoconazole has been used as the primary agent in five reported cases of osteomyelitis due to *C. albicans* with favourable clinical responses.[1] It is not associated with the undesirable, nephrotoxic side effects of intravenously administered amphotericin B and its ease of administration is an attractive feature.

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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 therapy 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. 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.

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

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®.

Cefoxitin has been observed in the milk of nursing mothers receiving the drug.

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

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
Transient eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia 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 have been reported.

Kidney
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 when required. (See complete monograph on ADMINISTRATION and RECONSTITUTION.)

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.

Usual Adult Dosage

Type of Infection	Daily Dosage	Frequency and Route
Uncomplicated forms* of infections such as pneumonia, urinary tract infection, soft tissue infection	3-4 g	1 g every 6-8 h I.V. or I.M.
Moderately severe or severe infections	6-8 g	1 g every 4 h or 2 g every 6-8 h I.V.
Infections commonly needing antibiotics in higher dosage (e.g. gas gangrene)	12 g	2 g every 4 h or 3 g every 6 h I.V.

*Including patients in whom bacteremia is absent or unlikely

Therapy may be started while awaiting the results of susceptibility testing.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Adults with Impaired Renal Function

MEFOXIN® may be used in patients with reduced renal function but a reduced dosage should be employed and it is advisable to monitor serum levels in patients with severe impairment.

In adults with renal insufficiency, an initial loading dose of 1 g to 2 g should be given. After a loading dose, the following recommendations for **maintenance dosage** may be used as a guide:

RENAL FUNCTION	CREATININE CLEARANCE mL/min	DOSE	FREQUENCY
Mild impairment	50-30	1-2 g	every 8-12 h
Moderate impairment	29-10	1-2 g	every 12-24 h
Severe impairment	9-5	0.5-1 g	every 12-24 h
Essentially no function	<5	0.5-1 g	every 24-48 h

In the patient undergoing hemodialysis, the loading dose of 1 - 2 g should be given after each hemodialysis, and the maintenance dose should be given as indicated in the Table above.

Neonates (Including Premature Infants), Infants and Children (See WARNINGS for Neonates under ADMINISTRATION in the complete monograph.)

Premature Infants with Body Weights Above 1500 g	20-40 mg/kg every 12 h I.V.
Neonates	
0-1 week of age	20-40 mg/kg every 12 h I.V.
1-4 weeks of age	20-40 mg/kg every 8 h I.V.
Infants	
1 month to 2 years of age	20-40 mg/kg every 6 h or every 8 h I.M. or I.V.
Children	20-40 mg/kg every 6 h or every 8 h I.M. or I.V.

In severe infections, the total daily dosage in infants and children may be increased to 200 mg/kg, but not to exceed 12 g per day.

MEFOXIN® is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

At present there is insufficient data to recommend a specific dosage for children with impaired renal function. However, if the administration of MEFOXIN® is deemed to be essential the dosage should be modified consistent with the recommendations for adults (see Table above).

PROPHYLACTIC USE

For prophylactic use, a three-dose regimen of MEFOXIN® is recommended as follows:

Vaginal or abdominal hysterectomy and abdominal surgery

2 g administered intramuscularly or intravenously just prior to surgery (approximately one-half to one hour before initial incision).

The second and third 2 g doses should be administered at 2-6 hour intervals after the initial dose.

Cesarean Section

The first dose of 2 g should be administered intravenously as soon as the umbilical cord has been clamped. The second and third 2 g doses should be given intravenously or intramuscularly four hours and eight hours after the first dose.

AVAILABILITY

MEFOXIN® is supplied as sterile powder in boxes of 10 vials:

3356 Ca - 1 g cefoxitin as sodium salt
3357 Ca - 2 g cefoxitin as sodium salt

Storage
MEFOXIN® in the dry state should be stored below 30° C.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(425-a,6,87x)

Studies of DNA Content in Cervical Intraepithelial Neoplasia by Cytologic and Histologic Flow Cytometry

B. Lambert, MD, FRCSC;* B. Barrette, MD;* Y. LePage, PhD†

Flow cytometry was done on 82 specimens of cervical cytologic scrapings and biopsies from patients with cervical intraepithelial neoplasia or condyloma. This study yielded significant results when compared with standard cytologic ($p < 0.01$) and histopathologic studies ($p < 0.05$). Histologic evaluation by flow cytometry required more examinations and did not give significant results. The authors conclude that cytologic flow cytometry, though not a replacement for standard cytologic examination, may be of help in establishing therapeutic strategies and follow-up protocols for patients with cervical precancerous conditions.

Un examen fluorocytométrique a été pratiqué sur 82 prélèvements cytologiques ou biopsies cervicales provenant de patientes porteuses de néoplasies intra-épithéliales cervicales ou de condylomes. Cette étude a révélé des différences significatives par rapport aux examens cytologiques ($p < 0.01$) et histologiques ($p < 0.05$) courants. L'évaluation histologique par fluorocytométrie a nécessité des examens plus nombreux et n'a pas apporté de résultats significatifs. Les auteurs concluent que même si la cytofluorocytométrie ne remplace pas l'examen cytologique standard, elle peut contribuer à l'établissement des stratégies thérapeutiques et du suivi clinique des patientes souffrant de pré-cancer cervical.

Abnormal DNA content is known to influence tumour aggressiveness and the malignant potential of cervical intraepithelial neoplasia (CIN).[1,2] We studied DNA indices by flow cytometry in relation to cytologic and histopathologic findings in patients with CIN.

We wanted to verify the clinical applicability of cytologic flow cytometry as a screening test for cellular malignancy, to evaluate the association between DNA content and histologic interpretation and to evaluate the malignant potential of the different degrees of CIN.

Patients and Methods

Patients with abnormal cervical smears were seen at colposcopy clinics for evaluation of CIN. Criteria for eligibility were: proposed conservative treatment for CIN and a lesion with a minimum surface area of 50 mm^2. Cervical scrapings were taken for the Papanicolaou test and for cytologic flow cytometry.

Originally, 97 patients underwent two cytologic examinations for evaluation of cytoploidy and one standard cytologic examination.

In 82 patients, two biopsies were taken using Kervorkian forceps — one for histologic diagnosis, the other for histologic flow cytometry. Controls chosen had negative Papanicolaou test results, no colposcopic aceto-white epithelium, and no punctate or mosaiform changes. Cytologic identification of a condyloma was the presence of cytoplasmic koilocytosis, with enlarged hyperchromatic nuclei and, histologically, the partial replacement of the cervical epithelium with koilocytes. Cytologic features of CIN were the presence, in variable quantities, of cervical cells with hyperchromatic nuclei and an increase in the nuclear–cytoplasmic ratio. The histologic features of CIN corresponded to those of progressive replacement of the cervical epithelium by malignant cells with an increased nuclear–cytoplasmic ratio varying in thickness from one-third of the epithelium in CIN grade I to two-thirds in CIN grade II and at least seven-eighths in CIN grade III.

In the laboratory, the specimens were processed to obtain a unicellular suspension. The spatula of the cervical scraping was washed with

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normal (0.9%) saline and fixed in 95% ethanol. The microbiopsy specimen was minced mechanically with a scalpel, passed through a 21 gauge needle, washed in normal (0.9%) saline, then fixed. Before staining with fluorochrome, fixed cells were treated with 0.5% pepsin for 8 minutes and then neutralized with TRIS-buffer. They were stained with propidium iodide for 20 minutes at 4°C. The cells were then passed through a 70-gauge nylon mesh filter and treated with ribonuclease. Normal human lymphocytes were used as normal diploid standard for the DNA content. Statistical analysis was by the χ^2 test.

Results

Cytoploidy and Cytologic Findings

Study of the association between cytologic and cytoploidy findings revealed that condyloma (HPV) and CIN grade III yielded the highest percentage of abnormal DNA content (70% and 64.7% respectively) as opposed to CIN I and normals (< 24%) (Table I).

Inversely, the normal content in condylomas and CIN III fell to 30% and 35.3% respectively. Despite the small number of patients in each group, comparison of CIN and condylomas with controls gave a significant result ($p < 0.01$). When CIN I and CIN II were compared with CIN III the difference was mildly significant ($p < 0.06$).

Cytoploidy and Histologic Findings

The same tests were applied when the cytoploidy findings were compared with the histopathologic findings (Table II). Condylomas and CIN III behaved differently ($p < 0.05$) from the milder degrees of CIN and controls. There was a significant difference ($p = 0.02$) between CIN I and CIN II versus CIN III, although the difference between CIN I versus CIN II and CIN III was not significant.

Table I. Association Between Cytoploidy and Cytologic Findings (N = 97)

	Cytologic findings, no. (%)				
Cytoploidy	**Controls**	**HPV**	**CIN I**	**CIN II**	**CIN III**
Normal	34 (77.3)	3 (30)	10 (76.9)	8 (61.5)	6 (35.3)
Abnormal	10 (22.7)	7 (70)	3 (23.1)	5 (38.5)	11 (64.7)
Totals	44	10	13	13	17

Table II. Association Between Cytoploidy and Histologic Findings (N = 82)

	Histologic findings, no. (%)				
Cytoploidy	**Controls**	**HPV**	**CIN I**	**CIN II**	**CIN III**
Normal	20 (76.9)	3 (42.8)	13 (76.5)	9 (75)	8 (40)
Abnormal	6 (23.1)	4 (57.2)	4 (23.5)	3 (25)	12 (60)
Totals	26	7	17	12	20

Table III. Association Between Histoploidy and Histologic Findings (N = 82)

	Histologic findings, no. (%)				
Histoploidy	**Controls**	**HPV**	**CIN I**	**CIN II**	**CIN III**
Normal	14 (73.7)	6 (54.5)	7 (63.6)	8 (61.5)	12 (42.9)
Abnormal	5 (26.3)	5 (45.5)	4 (36.4)	5 (38.5)	16 (57.1)
Totals	19	11	11	13	28

Histoploidy and Histologic Findings

Finally, when we compared biopsies by fluorocytometry to histopathologic findings (Table III), no significant difference was found. Contamination by normal stromal tissue underlying the cervical epithelium could be a factor in this unexpected finding.

Discussion

Our study showed that, compared with standard cytologic and histologic studies, flow cytometry, which assesses DNA content, gave significant results when condylomas and CIN III were compared with control specimens.

Similarly, Jakobsen and colleagues[3] found a majority (78%) of aneuploid cells in severe dysplasias and carcinomas in situ, in spite of diploidy in mild and moderate dysplasias. They then associated the aneuploidy index with both progressive and regressive characteristics. Tsou and colleagues[4] observed cluster cells in early S-phase region and a higher DNA content in 74.5% of patients who had condyloma.

We also found higher aneuploidy in condylomatous lesions, as if the viral infection was severely disturbing the DNA cellular content. Barres and associates[5] delineated tetraploidy indices as a demarcation between CIN grade I and CIN grades II and III. We found discrimination between CIN grades I and II and CIN grade III, but we conclude that cytologic flow cytometry is not really suitable for cytologic mass screening because we found abnormal patterns in 22% of control specimens but normal cells in 35% of CIN III specimens. It seems that the numerous abnormal cells in the latter indicate a greater malignant potential than in CIN I and CIN II. The fact that histologic flow cy-

tometry does not give significant results may be explained by the probable contamination of stromal tissue in the biopsies; this will have to be verified by control biopsies of normal areas in the vicinity of CIN. Further research is needed to refine flow cytometry; this technique should not be considered a replacement for cytology, but an aid in the clinical evaluation of CIN.

We thank Dr. J. Latreille for technical help and Dr. Harry Bard for reviewing the manuscript.

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BOOK REVIEWS

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range from plasma exchange and immunoadsorption to cryofiltration and in-vivo adsorption using incompatible red blood cell transfusions. The last article reports the effects of a new immunosuppressive agent, Spergualin, on the humoral immune system.

Overall, the book is an excellent reference manual for physicians interested in ABO-incompatible transplantation and is essential for anyone with research interest in xenotransplantation. It lacks the general overview and cohesiveness of a textbook but makes up for this by being up to date. The editors have included papers that present opposite viewpoints so that readers can formulate their own opinions on the controversial topics that surround ABO-incompatible transplantation.

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APPLICATIONS OF NONINVASIVE VASCULAR TECHNIQUES. Amil J. Gerlock, Jr., Vishan L. Giyanani and Carol Krebs. 541 pp. Illust. W.B. Saunders Company, Philadelphia; W.B. Saunders Company Canada Limited, Toronto, Ont., 1988. $93.60. ISBN 0-7216-2335-2.

This text provides an enormous amount of anatomic and physiologic data and describes in detail numerous noninvasive vascular techniques. There is excellent anatomic, angiographic and pathologic correlation. The role of duplex ultrasonography in extracranial carotid artery disease is adequately discussed, but its role in evaluating peripheral arterial and venous disease is understated. Other obvious omissions include colour-encoded Doppler and abdominal, pelvic and obstetric applications of noninvasive vascular techniques. The text is verbose and somewhat repetitive, particularly in the discussion of plethysmography evaluating cutaneous and digital perfusion. In many chapters, the number of figures and examples is excessive.

The description of instrumentation and Doppler principles is simple but too concise, and the use of nonstandardized terminology causes some confusion. The concept of aliasing is not explained or discussed and no references have been included at the end of this section.

The section on extracranial carotid arteries is organized, comprehensive and well referenced. High-quality, real-time ultrasound images and various spectral analysis patterns are included. The text refers to "frequency shift" based on a kilohertz scale, but the spectral images depict a velocity format, which is more meaningful clinically and should have been used throughout the text. Plaque morphology is well described and illustrated, but the limitation of duplex ultrasonography in the presence of heavily calcified plaque is not emphasized. Correlative duplex ultrasonography and angiography are nicely illustrated. The authors describe five categories of internal carotid artery stenosis but do not elaborate on how the grading system was derived. External carotid, common carotid and periorbital flow patterns are clearly explained.

The section on peripheral venous anatomy, flow hemodynamics, deep-vein thrombosis and venous insufficiency is well organized and beautifully illustrated. Nonimaging modalities, particularly photoplethysmography and strain-gauge plethysmography are emphasized.

An extensive, well-organized section describes systolic pressure measurements and indices and peripheral arterial waveforms as they pertain to aortoiliac and lower-extremity arterial disease. Again, nonimaging noninvasive techniques are emphasized but duplex ultrasonography is only mentioned briefly.

The section on upper-extremity anatomy and pathology is excellent. In this section the chapter on duplex ultrasonography of superficial masses, however, seems rushed and incomplete, and greater emphasis should be placed on its role in the assessment of patients after reconstructive vascular surgery.

This text is comprehensive, accurate,

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Prophylaxis of Deep-Vein Thrombosis in Total Hip Surgery

Richard Hu, MD

Thromboembolism is a common and serious complication of total hip replacement. Methods of prophylaxis include combinations of physical compression of the legs and anticoagulation. Results of treatment are difficult to document and quantitate. The authors reviewed 122 patients who underwent hip arthroplasty with intermittent pneumatic calf compression, intravenous administration of dextran and platelet inhibitors. In 20% of them, clinically suspected pulmonary embolism was confirmed by ventilation perfusion lung scanning. The true incidence of pulmonary embolism is probably greater than this and it appears that the prophylactic regimen used in this study does not confer any benefit.

La thromboembolie est une complication fréquente et grave de l'arthroplastie totale de la hanche. Les moyens prophylactiques comprennent diverses associations de compression physique de la jambe et d'anticoagulation. Les résultats de ces traitements sont difficiles à vérifier et à quantifier. Les auteurs ont étudié 122 patients qui ont subi une arthroplastie de la hanche avec compression pneumatique intermittente du mollet, administration intraveineuse de dextran et d'inhibiteurs de l'agrégation plaquettaire. Dans 20% des cas, une embolie pulmonaire cliniquement soupçonnée fut confirmée par scintigraphie pulmonaire de perfusion. L'incidence réelle des embolies pulmonaires est probablement supérieure à cela et il semble que le traitement prophylactique utilisé dans cette étude n'ait eu aucun effet favorable.

Deep-vein thrombosis and pulmonary embolism are major complications of total hip replacement. It is estimated that 40% to 60% of patients who do not receive prophylaxis will suffer deep-vein thrombosis.[1] Pulmonary embolism occurs in 10% to 15% of patients after hip replacement, and 1% to 2% of all those who undergo elective hip replacement will die if no prophylactic measure is used.[2]

The magnitude of thromboembolic disease has spurred clinicians to attempt to lower its incidence. Dextran has been used by many[3,4] and in combination with intermittent pneumatic compression of the legs has proven useful in preventing deep-vein thrombosis and, by inference, pulmonary embolism.

At one institution in Edmonton, dextran combined with intermittent calf compression was begun on an empirical basis for all patients admitted for total hip surgery. It is the aim of this paper to review the results of this regimen in terms of its effect upon the occurrence of pulmonary embolism.

Patients and Methods

A retrospective survey was done of all 122 patients admitted for total hip replacement surgery between January 1984 and December 1987. Charts were reviewed for pertinent aspects of patient history, physical examination, laboratory investigations, preoperative, intraoperative and postoperative care as well as diagnosis of thromboembolic disease and other complications.

All patients met the following criteria: they were operated on by one group of surgeons; they had pre- and postoperative prophylaxis for deep-vein thrombosis; the intraoperative management and surgical technique were similar; a cemented Charnley total hip replacement prosthesis was used.

The end-point of the study was clinically detectable pulmonary embolism proven by lung scanning.

Differences were analysed by Student's *t*-test.

Prophylactic Regimen

All patients were admitted to hospital at least 2 days before the operation and started on Persantine

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(Boehringer Ingelheim [Canada] Ltd., Burlington, Ont.) 50 mg three times daily. They were instructed on the postoperative use of the circoelectric bed and the intermittent pneumatic compression (IPC) boots.

The IPC apparatus (ALP 501; Twee Corp., Lake Oswego, Ore.) with a sterile boot was placed on the operative leg and a non-sterile boot on the opposite leg at the time of operation. Immediately postoperatively, 500 ml of dextran 70 solution was given intravenously. Over the next 3 days the patient was given a total of 1 litre of low molecular weight dextran (dextran 40).

Patients continued to have IPC of the calf for 1 week postoperatively. Weight bearing and active assisted physiotherapy were begun on postoperative day 2 or 3.

Results

Of the 122 patients, 60 met the inclusion criteria for further analysis. The remainder were excluded for various reasons (Table I).

Age, weight, sex, operating time, blood loss and volume of blood replacement were analysed (Table II). There was an equal distribution of male and female patients. Associated major medical problems occurred in 50% of patients.

In these 60 patients, 12 had clinically detected pulmonary emboli proven by lung scanning. There did not appear to be any statistically significant difference in these patients in any of the factors analysed compared with the nonembolism group.

Complications included three wound hematomas and three hip dislocations, two in the group of patients who had pulmonary embolism. There were no episodes of congestive heart failure and no allergic reactions to dextran. There were no postoperative deaths.

Table I. Reasons for Exclusion of Patients

Reason	No.
Hemiarthroplasty	18
Hybrid procedure	12
Revision	8
Noncemented prosthesis	16
Insufficient data	8
Total	62

Discussion

Many methods of prophylaxis have been used in an attempt to manipulate Virchow's triad of vascular stasis, blood hypercoagulability and vessel wall damage. Dextran is thought to alter blood coagulability through a number of mechanisms. Lowering of blood viscosity is important as is a slight heparin-like effect. Intermittent compression of the leg makes intuitive sense in that it directly affects the vascular stasis limb of the triad.

In our patients, those treated with dextran and IPC of the calf had a frequency of pulmonary embolism equal to that in previous reports of those who did not receive prophylactic measures.[2] The reasons for this high rate of pulmonary embolism can only be speculated upon. However, some factors in our patient population were of prime importance in thrombus production.

Surgical approach may have a bearing on the occurrence of embolism. The anterolateral approach with trochanteric osteotomy has been shown to produce more deep-vein thrombosis than the posterior approach.[1] This is possibly a result of the more extensive soft-tissue dissection required to reach the hip joint.

Type of prosthesis inserted may have a bearing upon thrombus production. Francis and associates[5] have reported a far higher incidence of deep-vein thrombosis in patients with cemented total hip prostheses than with noncemented ones. They believe that the type of prosthesis inserted may have more impact on thromboembolism than the prophylactic regimen.

Intermittent compression of the calf alone has little effect on those thrombi that originate in the thigh (approximately 20%). Full length compression of the limb is effective on its own and is a useful adjunct to thromboembolism prophylaxis.[2,4]

Conclusions

Intermittent pneumatic compression of the calf in association with dextran confers no benefit in patients who undergo cemented total hip replacement.

The empiric use of a therapeutic regimen should be monitored regularly to ensure that it is efficacious.

Table II. Factors Analysed in Patients With and Without Pulmonary Embolism

	Pulmonary embolism	
	Without (n = 48)	With (n = 12)
Age, yr	60.5	62.5
Weight, kg	77	72
Operating time, min	85	84
Blood loss, ml	540	518
Drop in hemoglobin, g/L	32	28
Blood replacement, units	2.4	2.5
No. with associated medical problems	23	6
Complications		
Hematoma	2	1
Dislocation	1	2

I thank Drs. Joseph and Paul Moreau and Dr. Paul Leung for allowing me to review their patients.

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BOOK REVIEWS

continued from page 206

practical and easy to read. Although it has a few limitations, it is an appropriate reference for anyone interested in learning noninvasive vascular techniques.

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THE BASIC SCIENCE OF VASCULAR SURGERY. Edited by Joseph M. Giordano, Hugh H. Trout, III and Ralph G. DePalma. 773 pp. Illust. Futura Publishing Co., Inc., Mount Kisco, New York, 1988. $89.00 (US). ISBN 0-87993-321-6.

Despite the recent publication of a number of textbooks of vascular surgery, this book fulfils a vital need because it presents under one cover information that has been spread through a number of publications, many of which are not readily available to the vascular surgeon. The editors are three senior vascular surgeons from the George Washington University Medical Center. Each of the 22 chapters is written by an expert in the field, including vascular surgeons, internists and anesthetists. The textbook covers the basic science and related clinical features of vascular embryology, the lymphatic system, endothelial cells, cerebrovascular disease and arteriovenous fistulas; the physiologic and biochemical events associated with mesenteric vascular insufficiency and infarction; the anatomy and physiology of male sexual function; the role of the carotid sinus and other baroreceptors; and arterial and vascular graft infections. Of value is the presentation, in an objective and mature fashion, of the controversial aspects of each topic, reflecting the authors' wide experience and knowledge of the subject.

In their introduction the editors state "Within three decades vascular surgery evolved into a unique specialty dedicated to treatment of patients with vascular diseases. Vigorous local and national certification in vascular surgery all attest to the maturation of a distinct discipline." Professor John Bergan summarizes the need for this book in his preface: "This volume identifies the components of basic sciences peculiar to vascular surgery, clarifies each and relates them to practice. Thus, vascular surgery which once was just technique and mechanics has become an intellectual endeavor as well."

Despite the number of authors, this book reads well. It should be in the library of all practising vascular surgeons and candidates for certification in vascular surgery, since it covers the basic science portion of this specialty, filling in the gaps in standard textbooks.

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ESSENTIAL SURGICAL PRACTICE. 2nd edition. Edited by A. Cuschieri, G.R. Giles and A.R. Moosa. 1438 pp. Illust. Butterworth International Edition, Stoneham, Mass., 1988. $125.00 (US). ISBN 0-7236-1127-0.

This textbook has been extensively modified and revised, and a new section on trauma has been added since its first edition.

The first section is devoted to general aspects of surgical disease and covers common surgical problems. I particularly liked the chapters on surgical infection, in which bacterial, viral, fungal and parasitic infections are discussed, the one on oncology, which covers chemotherapy and radiation and that on cutaneous disorders and malignancy, which will be of use to general surgeons who have to deal with these problems without the help of a dermatologist.

The eight chapters on the various aspects of trauma were written by North American authors, because it is acknowledged that this area of surgery is more fully developed on this continent. This section is particularly appropriate in light of the current interest in trauma training for surgical residents. The nine chapters on head and neck surgery provide a wider scope than most general textbooks on this subject and include chapters on nose and paranasal sinuses, the ear and ocular trauma. The general surgeon will find the chapters on intracranial emergencies, spinal injury and the surgery of pain of interest.

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Cefizox™

sterile ceftizoxime sodium

THERAPEUTIC CLASSIFICATION

Antibiotic

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

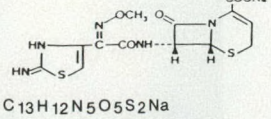
CHEMISTRY

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.

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Spontaneous Rupture of the Diaphragm in Labour: a Case Report

D.B. Ross, MD; G.E. Stiles, MD, FRCSC, FACS

Spontaneous rupture of the diaphragm during normal labour is extremely rare. It requires emergency surgical correction. The authors report what they believe is only the second reported case. Eleven hours after delivery of a male infant, a 27-year-old woman experienced severe epigastric pain, vomiting and dyspnea, followed by cardiopulmonary arrest. Although the ruptured diaphragm was diagnosed and repaired, she suffered severe anoxic encephalopathy and died 3 weeks after operation without regaining consciousness. Clinicians must be aware of the existence of this rare condition because failure to diagnose and treat the ruptured diaphragm will almost certainly lead to the patient's death.

La rupture spontanée du diaphragme durant le travail est extrêmement rare. Elle exige une correction chirurgicale immédiate. Les auteurs décrivent ce qu'ils croient être le deuxième cas rapporté seulement. Onze heures après la naissance d'un garçon, la mère de 27 ans souffrit de douleurs épigastriques intenses, de vomissements et de dyspnée, suivis d'un arrêt cardiorespiratoire. Malgré le diagnostic de rupture du diaphragme et sa réparation, la femme souffrit d'encéphalopathie anoxique grave et elle mourut 3 semaines après l'opération, sans avoir repris conscience. Les médecins doivent être sensibilisés à l'existence de cette affection rare car, faute d'avoir diagnostiqué et traité une rupture du diaphragme, le décès suivra presque invariablement.

Spontaneous rupture of the diaphragm during labour is extremely rare. To our knowledge only one such case has been reported.[1] We describe another case.

Case Report

A 27-year-old primigravid woman was delivered of a healthy 3640-g infant boy after a 20-hour labour at another hospital. The second stage was prolonged at 3 hours and vacuum extraction was necessary. Eleven hours after delivery, the woman complained of severe epigastric pain radiating to her left shoulder, associated with vomiting and shortness of breath. Thirty-two hours after delivery she had a full cardiopulmonary arrest on her way to the radiology department for a chest x-ray. She was successfully resuscitated, but it was approximately 1 hour before her blood pressure was restored. A chest x-ray film showed an air-fluid level in the chest on the left side. A tube thoracostomy was performed and gastric contents were drained. The patient was then transferred to our hospital.

On arrival, she was intubated, unresponsive and the pupils were in the mid-position. Blood pressure was 70/50 mm Hg, heart rate 95 beats/min and she was markedly cyanosed. Breath sounds were decreased on the left side. The initial arterial blood gas values demonstrated a metabolic acidosis with the pH 7.22, P_{O_2} 77 mm Hg, P_{CO_2} 22 mm Hg, HCO_3 10 mmol/L on F_IO_2 1.0. The chest x-ray film showed loops of bowel and stomach in the left hemithorax with deviation of the mediastinum to the right (Fig. 1).

The diagnosis of rupture of the left hemidiaphragm with herniation of abdominal contents was made and the patient was taken immediately to the operating room. At laparotomy the transverse colon, stomach and spleen were found in

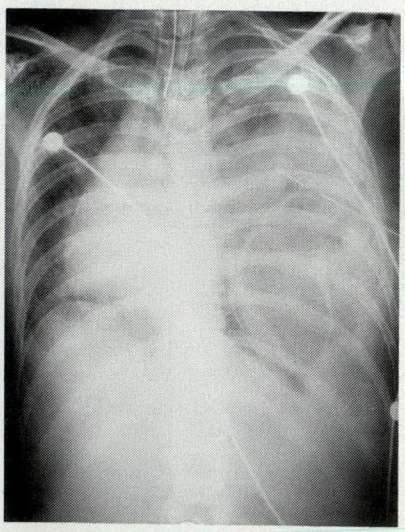

FIG. 1. Portable chest x-ray film demonstrating mediastinal shift to right, nasogastric tube in left chest and loop of bowel in left hemithorax.

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the left side of the chest. These were easily reduced and the small hole in the stomach caused by the chest tube was oversewn. There was a large fresh tear in the left hemidiaphragm extending from the hiatus to the posterolateral chest wall. This was closed with interrupted O Ethibond (Ethicon Ltd., Peterborough, Ont.) sutures.

Postoperatively, she showed signs of severe anoxic encephalopathy and did not regain consciousness. She died 3 weeks after admission from anoxic brain damage secondary to the initial cardiopulmonary arrest.

Discussion

Spontaneous rupture of the diaphragm during labour is extremely rare, only one other case having been reported in the literature.[1] Strangulation of abdominal viscera in a pre-existing congenital or traumatic diaphragmatic defect is more common, 21 such cases having been reported during pregnancy (16 congenital, 4 acquired, 1 spontaneous).[1-3]

Our patient's presentation was similar to the other reported case, that is, chest pain radiating to the left shoulder and progressive dyspnea. Unfortunately, the correct diagnosis was not entertained until the patient had sustained irreversible brain damage secondary to cardiopulmonary arrest, probably caused by the mediastinal compression.

The site of the rupture of the diaphragm in this case was the left posterolateral region which is the most common site for a ruptured diaphragm in blunt abdominal trauma, and is probably due to a congenital weakness in the area.[4] The fact that a fresh tear was present in the diaphragm with no apparent congenital defect suggests that the rupture was precipitated by the difficult labour and not by strangulation of viscera in a congenital defect. Both conditions are lethal if untreated.

Once suspected, the diagnosis is easily confirmed by chest x-ray. Pleural aspiration or decompression is unnecessary and dangerous. Salomon and associates[4] reported an iatrogenic injury to the spleen caused by this maneuver and our patient sustained a perforation of the stomach. Treatment consists of reduction of the herniated contents and suturing of the diaphragmatic edges through either a laparotomy or thoracotomy. In our opinion, laparotomy is the procedure of choice because it facilitates resection of any nonviable abdominal tissue.

Although uncommon, spontaneous rupture of the diaphragm or strangulation of abdominal viscera in a pre-existing diaphragmatic hernia during pregnancy are potentially lethal conditions and should be suspected in any pregnant or postpartum woman with chest pain and dyspnea.

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Undiversion in Patients With Meningomyelocele

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Since 1981, 12 patients with neurogenic bladder due to meningomyelocele who had had previous ileal conduit urinary diversions underwent assessment for undiversion. Two important criteria for undiversion were motivation and a reconstructable bladder. Four patients either did not fulfil these criteria or refused surgery. Eight patients (six females and two males) underwent undiversions. Ureteroureteral anastomosis was achieved in 13 ureters and ureteroneocystostomy in 2; transureteroureterostomy was necessary in 1 ureter. Augmentation cystoplasty and vesicourethropexy were important in establishing continence postoperatively; these procedures were not performed in two patients whose undiversion failed early in the series. The evolution of an investigation protocol, surgical technique and final approach to this complex problem are discussed.

Depuis 1981, 12 patients souffrant de vessie neurogène due à un méningomyélocèle et qui avaient subi une dérivation iléale du conduit urinaire ont été réévalués en vue de rétablir la continuité des voies urinaires. Deux critères importants étaient retenus pour justifier l'opération, soit la motivation du patient et la possibilité de reconstruire la vessie. Quatre patients n'ont pu rencontrer ces critères ou ont refusé la chirurgie. Huit patients (six filles et deux garçons) ont été opérés. Une anastomose urétéro-urétérale a pu être pratiquée sur 13 urétères et une urétéro-cystonéostomie sur 2; une transurétéro-urétèrostomie fut nécessaire pour 1 urétère. En vue d'obtenir la continence, il était important de pratiquer, en postopératoire, une cystoplastie de dilatation et une vésico-urétropexie; ces interventions n'ont pas été effectuées chez deux patients pour qui l'opération s'était soldée par un échec, tôt au début de la série. On commente l'évolution du protocole expérimental, de la technique chirurgicale et de l'approche finalement retenue pour corriger ce problème complexe.

The goals of urinary undiversion are to preserve renal function, to establish good bladder capacity and to preserve or establish continence.[1] With these goals in mind, in 1981 we embarked on a program to select patients with meningomyelocele for undiversion. At the British Columbia Children's Hospital, a multidisciplinary team of urologists, neurosurgeons, orthopedists, pediatricians, nurses, therapists and social workers have contributed to the assessment of patients with meningomyelocele. Twelve patients were selected as possible candidates for an undiversion. Four were deemed unsuitable because of low intelligence or unwillingness to undergo the procedure. The evolution of investigations considered necessary in preparation for undiversion and the surgical techniques employed have been an instructive process for us and are described.

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Patients and Methods

Undiversion was performed on six females and two males. All meningomyeloceles were lumbosacral or sacral. All patients were ambulatory, well-motivated and of normal intelligence, and all had undergone ileal conduit diversion in the late 1960s or early 1970s at ages ranging from 13 months to 6 years. A review of the indications for the initial diversion included frequent lower and upper urinary tract infections, progressive hydronephrosis or unmanageable incontinence (in older children). The long-term complications of ileal conduits are well known.[2,3] Four of our eight patients required stomal revision for stenosis, three had partial ureteroileal anastomotic obstruction (Fig. 1) and five suffered from recurrent pyelonephritis. One teenager found her ileal conduit with external appliance socially unacceptable.

Urologic evaluation included assessment of upper tracts, bladder and bladder outlet. Intravenous urograms and loopograms (retrograde

filling of ileal segment and ureters with Hypaque) were used to assess renal function and identify the length of the proximal ureter. Renal function was grossly normal (serum creatinine less than 100 μmol/L) in all patients; isotope renography was not routinely performed. Ureteral dilatation ranging from mild to severe was noted in 7 of 16 ureters.

All patients underwent cystoscopy and retrograde ureterography to identify the distal ureteral stump for measurement (Fig. 2). Ureteral stumps varied in length from 2 to 9 cm, with 13 having stump lengths of 4 to 6 cm. Cystoscopy revealed

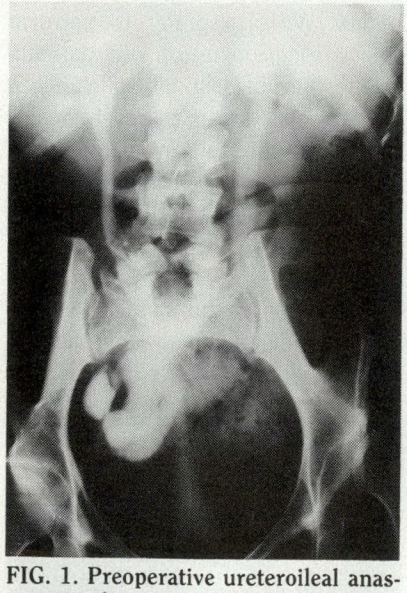

FIG. 1. Preoperative ureteroileal anastomotic obstruction with left-sided hydronephrosis.

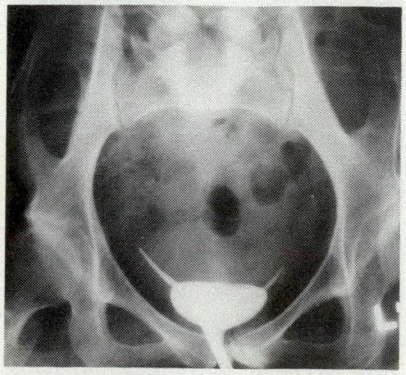

FIG. 2. Preoperative retrograde cystogram showing ureteral stump lengths of approximately 3 cm and 5 cm.

an incompetent bladder neck in all female patients. Voiding cystoureterography was performed if reflux was known to be a problem prior to diversion, although reflux in an undiverted bladder may not be important.[4]

Urodynamic tests were performed on all patients, with virtually all showing a poorly compliant bladder with a low urethral pressure profile. All had perineal electromyographic activity. Bladder cycling was initially attempted with a suprapubic cystocath and later in conjunction with the teaching of clean intermittent catheterization. Continent cycled volumes were less than 150 ml in four patients, 150 to 200 ml in two and 250 ml in two patients. Initially, we used these data to estimate which patients would need augmentation cystoplasty, but this approach failed and we now routinely perform this procedure.

Surgical Procedures

Undiversion involves re-establishing continuity of upper and lower urinary tracts, with or without augmentation cystoplasty or procedures to prevent incontinence. The initial procedure consisted of a ureteroureterostomy in 13 of the 16 renal units. Intraoperative placement of a ureteral stent to identify the stump greatly facilitated this, since the proximal end of the distal stump was otherwise difficult to identify because of the dense scar tissue. Transureteroureterostomy was performed in one case because of a short (2 cm) distal stump and because the proximal ureter was not long enough to be reimplanted into the bladder. In another patient, two grossly dilated ureters secondary to ureteroileal anastomotic obstruction required trimming and reimplantation into an augmented bladder.

Neither of the two male patients underwent a procedure to prevent incontinence. Both were undiverted after puberty (at 17 and 21 years) in the anticipation that normal bladder neck growth would aid in continence. A standard Burch vesicourethropexy was performed on four of the six female patients to prevent incontinence. The first two females, who did not undergo a vesicourethropexy, were both incontinent postoperatively. We now perform Burch repairs on all females.

Our initial surgical approach with augmentation cystoplasty is summarized in Table I. Bladders were augmented with the ileal conduit, in most cases as a cupped patch opened on the antimesenteric border and sutured to the superior surface of the open bladder. These patients were selected for augmentation because of a small capacity bladder on cycling.

Results

Early complications of undiversion were minimal. They included one wound infection, two persistent

Table I. Cycled Bladder Capacities

Patient no.	Sex	Augmentation cystoplasty	Cycled capacity, ml
1	F	Yes, own loop	100
2	M	Yes, ileum	100 – 150
3	F	Yes, own loop	100 – 150
4	F	Yes, own loop	150 – 200
5	F	No	200 – 250
6	F	No	200 – 250
7	M	No	150 – 200
8	F	No	100 – 150

leaks (one ureteral, one ileal cystoplasty) managed by conservative means and one urinary tract infection due to *Pseudomonas* sp that was difficult to eradicate because of multiple antibiotic resistance. There were two early failures (patients 6 and 8, Table II). Both were incontinent and had vesicoureteral reflux. Neither had undergone augmentation cystoplasty or vesicourethropexy. Initially, patient 5 did well, but increasing incontinence developed associated with uterine prolapse. Cycled bladder capacities in patients 5 and 6 were good before undiversion and they were selected to forgo augmentation cystoplasty (Table I). All three of these patients were managed early in our series and none underwent anti-incontinence or augmentation procedures. Patients 5 and 6 had augmentation ileocystoplasties and Burch vesicourethropexies, which in the case of patient 5 was a repeat procedure with bladder neck reconstruction.

Our final results are listed in Table II. Both male patients were continent using anticholinergic drugs. Four of the six females were continent (three without anticholinergics). Two patients continued to have problems: patient 8 had to catheterize herself every 2 hours to avoid incontinence and patient 4 had stress incontinence, not considered serious enough to warrant further surgery.

Follow-up ranged from 48 to 72 months. Follow-up intravenous pyelography or ultrasonography showed improvement or resolution of hydronephrosis in all the ureters that were markedly dilated preoperatively (Fig. 3).

All patients were taking low-dose antibiotics prophylactically. One patient had two episodes of cystitis, but there was no episode of pyelonephritis and no deterioration in renal function. Two patients suffered mucus retention necessitating an emergency room visit early after hospital discharge. Both were catheterized and more than 700 ml of urine drained, indicating the success of augmentation cystoplasty.

Discussion

Undiversion has clearly emerged as a viable option for patients with meningomyelocele who have previously undergone supravesical diversion, provided they are carefully selected. The extent of our assessment of these patients has been modified by our management experience.

Bladder cycling was initially performed by way of a suprapubic cystocatheter, but it became evident that this could be more readily accomplished in conjunction with the teaching of clean intermittent catheterization. Moreover, the cycled capacity eventually reached was not predictive of good operative results in terms of continence. We now augment all bladders in this type of patient regardless of cycled capacity. Perlmutter[5] rejected patients for undiversion who had severe incontinence and small bladder capacity after cycling, apparently because of the complexity of augmentation cystoplasty and urethrovesical suspension. However, we found that the ileal conduit can usually be readily mobilized into the pelvis and used to augment the bladder.[6,7] Similarly, a simple Burch vesicourethropexy does not add complexity or time to the operation and has been successful in our hands. We also prefer to perform this suspension on all our patients at the time of original undiversion. Our patients are prepared to maintain clean intermittent catheterization for life as a consequence of their original affliction and so bladder emptying problems are not a concern.[8]

In summary, our clinical experience has modified our approach to undiversion in patients with menin-

Table II. Results of Postoperative Undiversion

Patient no.	Clean intermittent catheterization, h	Mean volume, ml*	Continence	Anticholinergic agent
1	3	300	Yes	No
2	4	250	Yes	Yes, Ditropan
3	3	350	Yes	Yes, Tofranil
4	3	250	Stress incontinence	Yes, Tofranil
5	4	250	Yes	No
6	3	250	Yes	No
7	3	250	Yes	Yes, Ditropan
8	2	150	No	Yes, Ditropan

*Continent volumes not maximum volumes.

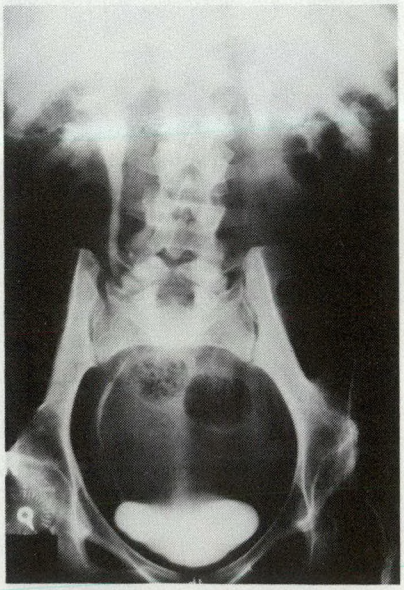

FIG. 3. Postoperative ureteroureterostomy and resolution of left-sided hydronephrosis approximately 6 months after undiversion.

gomyelocele. We prefer to augment all bladders and perform a Burch vesicourethropexy on all our female patients. Ipsilateral ureteroureterostomy is almost always possible; one available intraoperative option includes transureteroureterostomy. Although this is primarily a cosmetic operation resulting in improved quality of life and a better body image, the resolution of hydroureteronephrosis and absence of upper tract infections in our patients suggest that it provides some protection from future deterioration in renal function.

We thank Drs. G. Coleman and J. Masterson for allowing us to include their patients in this study.

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BOOK REVIEWS

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Thoracic and cardiac surgery are well covered and contain the core of knowledge needed by surgical trainees. Mesenteric vascular disease, which, in the past, has been poorly understood and treated, is a welcome addition to the section on vascular diseases. Fortunately, this condition is increasingly being diagnosed before laparotomy and appropriate preoperative investigations are being performed. The topics covered in most general surgery textbooks are considered in the section on general surgery. There are also chapters on organ transplantation, surgery for vascular access and peritoneal dialysis, and gynecology. The last section, on genitourinary surgery, covers topics clearly.

To the editors' credit, one is not aware of changes in style between authors. Photographs and x-rays clearly illustrate the points made, and the many line diagrams are of excellent quality. Of interest is that many chapters end with a prediction as to the direction in which the field is heading. The bibliography is adequate and predominantly from the 1980s.

The authors state that their intention is to provide an organized, up-to-date account of modern surgical practice, covering the core material for those preparing for postgraduate examinations. I believe that they have done this in a very readable form. The book is not intended to be a reference book for the surgeon, but I found much useful information, particularly in those areas in which I do not regularly deal. I recommend the book for general surgeons in the core years of their training.

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PRINCIPLES OF ORGAN TRANSPLANTATION. Edited by M. Wayne Flye. 687 pp. Illust. W.B. Saunders Company, Philadelphia; W.B. Saunders Company Canada Limited, Toronto, 1989. $180.00. ISBN 0-7216-1323-3.

Transplantation is a surgical specialty in continuous evolution as principles are modified by new concepts, better understanding and research. This book, written by 57 contributors who are well known in their fields, reflects the opinions and experience of many transplantation centres in the United States and France.

The first section of the book is a review of basic science aspects of immunology. The authors describe the immune system in its two parts, the cellular and the humoral. They cover new concepts of cellular interaction with antigen, immunoglobulin structure and lymphokine function. The major histocompatibility complex is well described with its class I and II antigens. Two other chapters are dedicated to immunobiology — one on immunohematology, the second on effects of blood transfusion in transplantation. These are excellent reviews of the importance of blood-group antigens in transplantation. The immunologic aspect of blood transfusion and its clinical application in renal allografts is also mentioned.

The second section describes the basic principles of transplantation, including immunogenetics, immune regulation and methods of histocompatibility testing. The author mentions all possible immunologic tests identifying the most important and applicable in clinical use. Pre- and post-transplant serologic tests to improve recipient selection and predict graft survival are also described. The rejection phenomenon, its immunobiologic features, mechanism and specific pathologic characteristics regarding the kidney, liver, heart and lungs, is also explained in this section. Finally, the main author presents a good review of immunosuppressive therapy, the drugs and methods used in

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ℙPRIMAXIN®

(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.

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

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:

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

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

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

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

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Difficult Implant Retrieval: a Case Report

Hugh U. Cameron, MB, ChB, FRCSC

Artificial joint prostheses can be expected to fail eventually. The author describes the case of a woman whose cemented knee-joint hinge prosthesis failed and required revision. This prosthesis was designed so that the stem became thinner as it approached the bearing surfaces. As a result the implant could not be removed from the cement and the cement could not be removed without severe destruction of surrounding bone. Although this prosthesis is no longer being used, there may be patients having this implant who will require revision in the future. This paper warns surgeons that its removal will be extremely difficult and appropriate plans should be made preoperatively. The author concludes that no stemmed implant should be cemented in place if it cannot readily be removed from the cement.

On peut toujours s'attendre à la défaillance éventuelle des prothèses d'arthroplastie. L'auteur décrit le cas d'une femme dont la prothèse à charnière du genou, cimentée à l'os, fit défaut et nécessita une révision. Cette prothèse était conçue de façon à ce que la tige soit plus mince à proximité des surfaces d'appui. Il en suivit que l'implant ne pouvait être dégagé du ciment et que le ciment ne pouvait être enlevé sans causer une importante destruction de l'os adjacent. Bien que cette prothèse ne soit plus en utilisation, certains patients peuvent encore en être porteurs et devoir faire l'objet d'une révision future. Cet article vise à informer les chirurgiens que l'enlèvement de ces prothèses se révélera extrêmement difficile et qu'une bonne planification préopératoire s'impose. L'auteur conclut qu'un implant à tige ne devrait jamais être cimenté en place s'il ne peut être dégagé du ciment.

Although the short-term success rate of artificial joint replacement is high, the predictions from Sweden[1] suggest that all joints will eventually fail. Revision, therefore, should be anticipated and implants designed to allow a quick, simple, change of prosthesis because soft-tissue scarring and loss of bone stock will make the surgery difficult enough.

I recently encountered a case in which the implant violated these precepts; revision was extremely difficult and a multistage revision was required.

Case Report

A 65-year-old woman had injured her knee in 1937. She had undergone a number of subsequent operations and at one of these a hinge prosthesis had been inserted and a patellectomy performed. The tibial stem on the hinge prosthesis fractured. This was revised to an un-

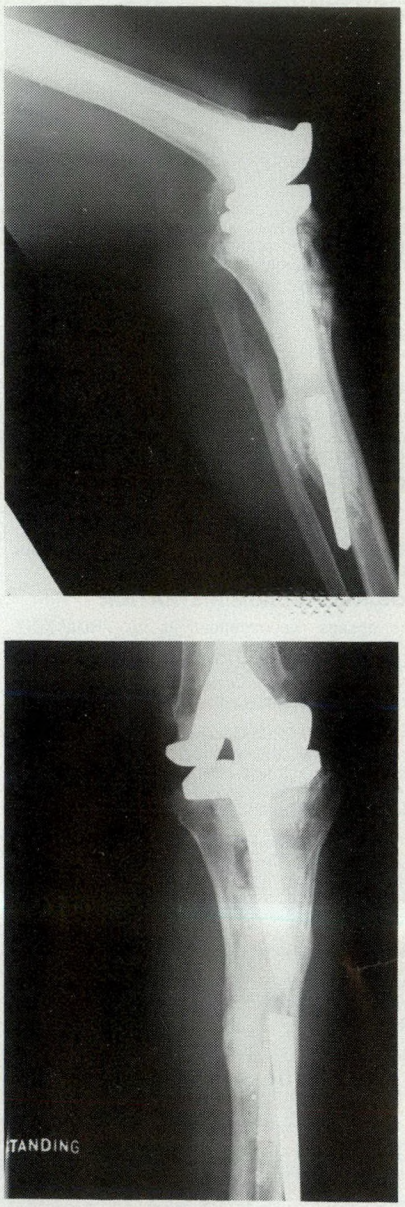

FIG. 1. Broken stem of original hinge prosthesis can clearly be seen. Some radiolucency surrounds tibial component which was relatively loose. There is no femoral radiolucency and femoral component was firmly fixed to bone.

From the Department of Surgery, The Orthopaedic and Arthritic Hospital, University of Toronto, Toronto, Ont.

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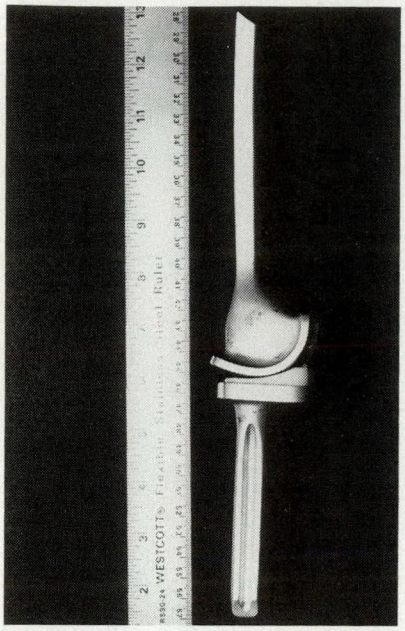
Reprint requests to: Dr. H.U. Cameron, 318 – 43 Wellesley St. E, Toronto, Ont. M4Y 1H1



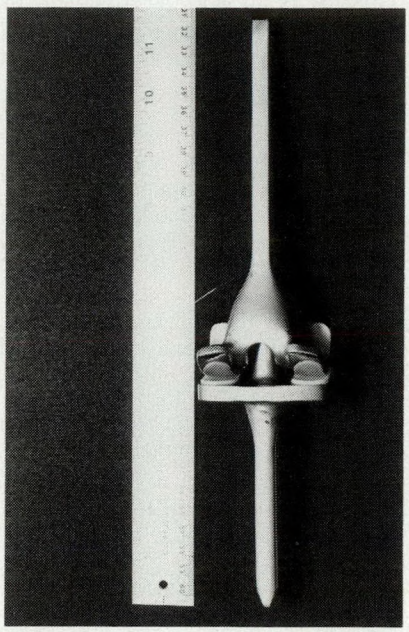


FIG. 2. What was not realized before removal of prosthesis was that femoral component was thicker proximally than distally, thus making extraction by longitudinal driving impossible. Distal femur was severely damaged in extraction of stem.

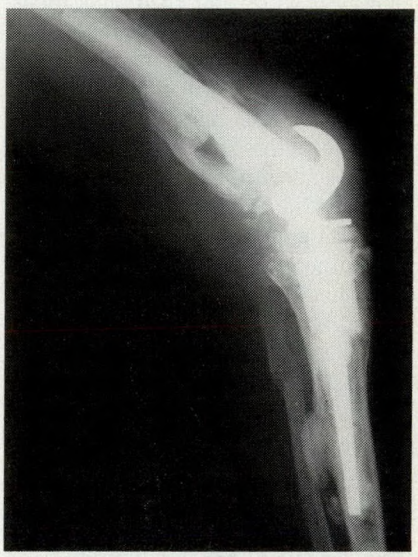


FIG. 3. After two sessions of allografting, length was restored. Guepar long stem was cemented in place. It was necessary to cement these stems in order to gain stability to allow healing of grafts.

linked type of hinge prosthesis (Fig. 1).

When seen, she had severe patellar tendon symptoms probably because the implant had no anterior femoral condylar bearing flange. She also had tibial pain from mild loosening of the tibial stem.

During revision surgery, the tibial component and broken tibial stem and cement were fairly easy to remove, but the femoral side simply could not be extracted by conventional methods. The cement was broken up as far as possible with curved osteotomes, but the bone, which was thin and osteoporotic, began to disintegrate long before the stem tip was reached. When the femoral stem was eventually extracted it was found to be widened proximally in both planes (Fig. 2) (i.e., it was wedge shaped in the wrong direction). Attempts to remove the implant simply tightened it in place.

A long-stem Guepar II hinge was inserted to act as an internal splint and the patient was placed in traction. Four weeks later, extensive allografting was carried out around the Guepar II stems. The allografts were allowed to heal for 9 months then the knee was again opened. Much of the allograft had united, but further extensive grafting was needed to restore length; the Guepar II stems were then cemented in place (Fig. 3).

Comment

This case illustrates one of the truths of orthopedic surgery; if a prosthesis cannot be extracted from cement, the cement cannot be removed without splitting the bone. Had the reverse wedge nature of the prosthesis in this patient been recognized before surgery, a formal split of the femur should have been performed removing a huge window for later replacement.

This prosthesis is obsolete. However, there may still be patients who have this implant and will need revision surgery in the future. The moral of this case report is quite clear: a prosthesis should never be inserted if it cannot easily be removed.

Reference

1. RYD L: Micromotion in knee arthroplasty. A roentgen stereophotogrammetric analysis of tibial component fixation. *Acta Orthop Scand Suppl* 1986; 220: 1–80

clinical practice and their indications, mode of action and side-effects.

The third section is on the major organs transplanted in clinical practice. The largest part, on renal transplantation, covers the causes of chronic renal failure and methods of dialysis and describes the technique and indications for creating an arteriovenous fistula. The authors then describe the mode of assessment of donors and recipients in renal transplantation. Immunosuppressive therapy, mainly with cyclosporine, corticosteroids and anti-lymphocyte globulin, and their side-effects, is discussed. Infectious complications in renal transplant patients are well described in one chapter that covers cause, diagnosis and treatment. Finally, the follow-up of patients is studied and an overview provided of the differential diagnosis in the rejecting kidney allograft.

Transplantation of other organs is also described by different authors, well known in their fields. Each author presents a historical review, followed by clinical and research information and own experience. Chapters on liver, pancreas, bone marrow, heart and lungs are interesting because they offer the reader general concepts in an understandable manner. However, each is based solely on the techniques and practice of the author's centre.

In the final section, information on the criteria of brain death, selection of donors, organ preservation and anesthesiology are discussed. The risk of malignant disease in the transplant patient is also covered.

Overall, the book is a good reference for physicians and fellows interested in organ transplantation.

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BOOKS RECEIVED

This list is an acknowledgement of books received. It does not preclude review at a later date.

Decision Making in Surgery of the Chest. Edited by Laurens R. Pickard. 168 pp. Illust. W.B. Saunders Company Canada Limited, Toronto, 1989. $107.95. ISBN 0-7216-1168-0.

Disorders of the Spleen. Pathophysiology and Management. Edited by Carl Pochedly, Richard H. Sills and Allen D. Schwartz. 464 pp. Illust. Marcel Dekker, Inc., New York, 1989. $125.00 (US). ISBN 0-8247-7933-9.

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 India I Knew. Experiences of a Canadian Orthopaedic Surgeon Over 50 Years. W.J. Virgin. 176 pp. Illust. Britannia Printers Inc., Toronto, 1988. Price not stated.

Low Level Laser Therapy. A Practical Introduction. T. Ohshiro and R.G. Calderhead. 143 pp. Illust. John Wiley & Sons Ltd., New York, 1988. Price not stated. ISBN 0-471-91956-X.

Second Opinion. What's Wrong With Canada's Health-Care System and How to Fix It. Michael Rachlis and Carol Kushner. 371 pp. Collins Publishers, Toronto, 1989. $26.95. ISBN 0-00-215441-2.

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.

Textbook of Microsurgery. Edited by G. Brunelli. 1038 pp. Illust. Masson, Milano, 1988. Price not stated.

Dalacin® C Phosphate Sterile Solution

(clindamycin phosphate)

Antibiotic

Recommended Applications

Action: Clindamycin exerts its antibacterial effect by causing cessation of protein synthesis and also by causing a reduction in the rate of synthesis of nucleic acids.

Indications: Dalacin C Phosphate (clindamycin phosphate) is indicated for the treatment of infections where the oral route is not indicated or feasible.

Dalacin C Phosphate is indicated in the treatment of serious infections due to sensitive anaerobic bacteria, such as *Bacteroides* species, *peptostreptococcus*, anaerobic streptococci, *Clostridium* species and micro-aerophilic streptococci.

Dalacin C Phosphate is also indicated in serious infections due to sensitive Gram-positive organisms (staphylococci, including penicillinase-producing staphylococci, streptococci and pneumococci) when the patient is intolerant of, or the organism resistant to other appropriate antibiotics.

Warnings: Some cases of severe and persistent diarrhea have been reported during or after therapy with Dalacin C Phosphate (clindamycin phosphate). This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis. When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

If significant diarrhea occurs during therapy, this drug should be discontinued or, if necessary, continued only with close observation. Significant diarrhea occuring up to several weeks post-therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended. Mild cases showing minimal mucosal changes may respond to simple drug discontinuance. Moderate to severe cases, including those showing ulceration or pseudomembrane formation, should be managed with fluid, electrolyte, and protein supplementation as indicated. Corticoid retention enemas and systemic corticoids may be of help in persistent cases. Anticholinergics and antiperistaltic agents may worsen the condition. Other causes of colitis should be considered.

Contraindications: The use of Dalacin C Phosphate (clindamycin phosphate) is contraindicated in patients previously found to be hypersensitive to this compound, the parent compound, clindamycin, or clindamycin palmitate. Although cross-sensitization with Lincocin® (lincomycin hydrochloride) has not been demonstrated, it is recommended that Dalacin C Phosphate not be used in patients who have demonstrated lincomycin sensitivity.

Until further clinical experience is obtained, Dalacin C Phosphate is not indicated in the newborn (infants below 30 days of age), or in pregnant women. Studies indicate a toxin(s) produced by *Clostridia* (especially *Clostridium difficile*) may be a principal cause of clindamycin and other antibiotic-associated colitis. These studies also indicate that this toxigenic *Clostridium* is usually sensitive *in-vitro* to vancomycin. When 125 mg to 500 mg of vancomycin were administered *orally* four times a day for 5 - 10 or more days, there was a rapid observed disappearance of the toxin from faecal samples and a coincidental recovery from the diarrhea.

It should be noted that serious relapses have occurred up to one month after apparently successful treatment. A relatively prolonged period of continuing observation is therefore recommended.

Precautions: Dalacin C Phosphate (clindamycin phosphate), like any drug, should be prescribed with caution in atopic individuals. Dalacin C Phosphate must be diluted for intravenous administration. (See Dosage and Administration) The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

As with all antibiotics, culture and sensitivity studies in conjunction with drug therapy should be performed.

Since abnormalities of liver function tests have been noted occasionally in animals and man, periodic liver function tests should be performed during prolonged therapy. Blood counts should also be monitored, during extended therapy.

Dalacin C Phosphate may be used in anuretic patients. Since the serum half-life of clindamycin in patients with impaired hepatic function is greater than that found in normal patients, the dose of Dalacin C Phosphate should be appropriately decreased. Hemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Periodic serum levels should be determined in patients with severe hepatic and renal insufficiency.

Adverse Reactions: ***Local***

(a) *Intramuscular Injections:* Of 404 patients treated with Dalacin C Phosphate (clindamycin phosphate) intramuscularly (with a solution containing 150 mg/mL), six (1.5%) demonstrated local reactions as follows: Two complained of pain at the injection site, two demonstrated induration at the injection site and two developed sterile absesses.

(b) *Intravenous Infusions:* Of 192 patients with Dalacin C Phosphate by intravenous infusion, 14 (7.3%) demonstrated local reactions. Eleven patients developed superficial thrombophlebitis and one patient developed both superficial and deep thrombophlebitis. The majority of these cases developed in conjuction with the use of indwelling I.V. catheters and it is difficult to know how much the drug contributed to the irritation. Two patients developed localized erythema, swelling and pain at the site of the infusion.

Systemic Side Effects: Twenty-eight patients of 596 treated with Dalacin C Phosphate (clindamycin phosphate) by either the intramuscular or intravenous routes developed systemic side effects as follows:

	Number of Patients
Rash	7
Urticaria	1
Pruritus	1
Fever, Leucocytosis	1
Nausea, with or without vomiting	1
Diarrhea (See also under "Warnings")	4
Hypotension	1
Hypertension	1
Shortness of Breath	1
Superinfection*	4
Cardiac arrest**	1
Bad or bitter taste in mouth	5

* Superinfection is a complication of antibiotic therapy in general and is not necessarily a true side effect of clindamycin phosphate.

** Due to underlying myocarditis in this patient.

Clinical and Laboratory Findings: Patients treated during clinical trials of Dalacin C Phosphate (clindamycin phosphate) were followed with clinical laboratory tests, including complete hematology, urinalysis and liver and kidney function tests. Some of these tests were abnormal initially and returned to normal during therapy with Dalacin C Phosphate, while others were normal initially and became abnormal during therapy. Overall evaluation of clinical laboratory values in these patients does not indicate that Dalacin C Phosphate therapy has a toxic effect on the hematopoietic, hepatic or renal systems. Transient elevations of serum transaminases have occured in some patients, but other liver function tests (alkaline phosphatase, serum bilirubin) have not shown any tendency to increase and there have not been clinical signs of drug-induced hepatic toxicity.

Symptoms and Treatment of Overdosage: No cases of overdosage have been reported. No specific antidote is known. Doses as high as 1200 mg every six hours (4800 mg/day) by infusion for five days have been given without adverse effects.

DOSAGE AND ADMINISTRATION

Adults:

Intramuscular Injection: 600 mg/day in 2 equal doses.

Moderately severe infections: 600 to 1200 mg/day in 2 or 3 equal doses.

Severe infections: 1200 to 2400 mg/day in 2, 3 or 4 equal doses. Intramuscular injections of more than 600 mg into a single site are not recommended.

Intravenous Administration: Dalacin C Phosphate (clindamycin phosphate) must be diluted prior to I.V. administration to a concentration of 600 mg in 50 mL of diluent (12 mg/mL or less) and infused in not less than 10 minutes. Administration of more than 1200 mg in a single 1 hour infusion is not recommended. Dalacin C Phosphate should not be injected intravenously undiluted as a bolus.

Moderately severe infections: 900 to 1800 mg/day by continuous drip or in 2 or 3 equal doses, each infused over 20 minutes or longer.

Severe infections: 1800 to 2700 mg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer. In life-threatening infections, doses of 2700 to 4800 mg/day by continuous drip or in 3 or 4 equal doses each infused over 20 minutes or longer may be given.

Dilution and infusion rates:

Dose	*Diluent*	*Time*
300 mg	50 mL	10 min.
600 mg	50 mL	20 min.
900 mg	100 mL	30 min.
1200 mg	100 mL	45 min.

Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous I.V. infusion as follows:

To maintain serum clindamycin levels	*Rapid infusion rate*	*Maintenance infusion rate*
Above 4 mcg/mL	10 mg/min. for 30 min.	0.75 mg/min.
Above 5 mcg/mL	15 mg/min. for 30 min.	1.00 mg/min.
Above 6 mcg/mL	20 mg/min. for 30 min.	1.25 mg/min.

Children (Over one month of age)**:**

Intramuscular injection: 10 to 15 mg/kg/day in 2, 3 or 4 equal doses.

Moderately severe infections: 15 to 20 mg/kg/day in 3 or 4 equal doses.

Severe infections: 20 to 30 mg/kg/day in 3 or 4 equal doses.

Intravenous Administration: *Moderately severe infections:* 15 to 25 mg/kg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer.

Severe infections: It is recommended that children be given no less than 300 mg/day regardless of body weight.

Preparation for Intravenous use: 4 mL (600 mg) Dalacin C Phosphate when diluted with 1000 mL of the following commonly used infusion solutions was found to be physically compatible and demonstrated no significant change in pH or antimicrobial potency over a period of 24 hours:

Sodium chloride injection
Dextrose 5% in water
Dextrose 5% in saline
Dextrose 5% in Ringer's Solution
Dextrose 5% in half-strength saline plus 40 mEq potassium chloride
Dextrose 2½% in Lactated Ringer's Solution (Hartman's Solution)

Compatibility with other products: Dalacin C Phosphate was not stable when added to Dextrose 5% in water plus vitamins. Therefore it is not recommended that Dalacin C Phosphate be mixed with any infusion solution containing B vitamins. Dalacin C Phosphate has been shown to be compatible with Gentamicin sulfate, Tobramycin sulfate and Amikacin sulfate.

Composition: Each mL of Dalacin C Phosphate Sterile Solution contains Clindamycin phosphate equivalent to clindamycin base 150 mg, Benzyl alcohol 5 mg, Disodium edetate 0.5 mg, Water for injection q.s. When necessary the pH is adjusted with sodium hydroxide and/or hydrochloric acid to maintain a pH range of 5.5 to 7.0.

Dosage forms:

Availability: Dalacin C Phosphate Sterile Solution is available in 2 mL and 4 mL ampoules as well as a 6 mL vial.

Pharmacy Bulk Vial: Dalacin C Phosphate Sterile Solution is also available in a 60 mL Pharmacy Bulk Vial. The availability of the Pharmacy Bulk Vial is limited to hospitals with a pharmacy based IV admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing for intravenous use only.

NOTE: Do not store below 15°C.

Product Monograph available upon request. CE 1377.D

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GENERAL SURGEON: BC – Well-established general surgical practice for sale in choice lower mainland location. Canadian fellowship required. Reply in confidence with curriculum vitae to: **Box 800, Canadian Journal of Surgery, PO Box 8650, Ottawa, ON K1G 0G8.** –S89-13

GENERAL SURGEON AND ORTHOPEDIC SURGEON: BC – For thriving BC sunshine coast community of 20 000 on the doorstep of Desolation Sound. Fully accredited 140-bed hospital under construction. Medical staff includes 17 GPs, 4 GP anesthetists, internist, pediatrician and 2 surgeons. Excellent year round recreation and cultural attractions include boating, fishing, golfing, modern indoor recreation theatre complex and community college. Frequent daily air and ferry connections to Vancouver. Contact: **Dr. B.K. Cutler, Department of Surgery, Powell River General Hospital, 5871 Arbutus Ave., Powell River, BC V8A 4S3. Tel: (604) 483-3211.** –S89-10

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

SPINAL SURGERY FELLOWSHIP: ON – Available July 1, 1989 and July 1, 1990, Department of Surgery, Division Orthopedic Surgery, University of Western Ontario, London. For information contact: **Stewart I. Bailey, MD, FRCSC, 345 Westminster Ave., London, ON N6C 4V3. Tel: (519) 439-0701.** –S89-11

CHIEF, DEPARTMENT OF SURGERY: ON – The Ottawa Civic Hospital, a 922-bed tertiary care, teaching and research institution, closely associated with the University of Ottawa, invites applications for the position of Chief of the Department of Surgery. The Department and its appointments are closely linked to the University of Ottawa Department of Surgery. Applicants must have a Royal College of Physicians and Surgeons Fellowship in a surgical subspecialty and have achieved, or be a candidate for, appointment at the associate or full professor level at the University of Ottawa. Previous administration and clinical or basic research experience is essential. The hospital is rapidly expanding its research efforts in two campus research institutes. The recruitment of new clinician scientists in hospital division is a priority and University, Hospital and Department of Research resources are dedicated to this. Several division head positions are now open and the new Chief is to be involved in recruitment. In accordance with Canadian immigration policies, initial preference for this position will be given to Canadian citizens and permanent residents of Canada. Please reply with curriculum vitae, and names of three referees, to: **Dr. J.D. Grimes, senior vice president, Research and Clinical Administration, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, ON Canada K1Y 4E9. Tel: (613) 761-4614.** –S89-15

CHAIR OF UROLOGY: ON – Applications are invited for the position of Chairman of the University Division of Urology, University of Ottawa, School of Medicine. The Children's Hospital of Eastern Ontario, the Ottawa Civic Hospital and the Ottawa General Hospital are participating institutions which offer excellent resources to a Urology Training Program which is fully approved by the Royal College of Physicians and Surgeons of Canada. There is a complement of 14 urologists with university appointments, of which 6 are GFTs; currently the Division of Urology has an establishment of 9 residents in training. The successful candidate shall be a certified specialist of the Royal College of Physicians and Surgeons of Canada and be eligible for licensure by the College of Physicians and Surgeons of Ontario. Candidates will have a proven record in clinical and academic urology. While the position requires a major leadership role in the university/hospital/community settings, preference will be given to a qualified individual devoted to the pursuit of academic excellence in teaching and research. Part of the mandate will focus on the development of research in urology and continuing quality teaching programs at both the undergraduate and postgraduate levels. The successful candidate will hold a joint appointment as Chairman of the University Division of Urology and Head of Urology at one of the teaching hospitals. Salary and fringe benefits are commensurate with qualifications and experience and are in accordance with existing academic scales at the University of Ottawa. In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. Employment equity is University policy. Applicants are requested to forward their curriculum vitae and the names of three referees, prior to June 1, 1989, to: **Gilles D. Hurteau, MD, dean - School of Medicine, University of Ottawa, 451 Smyth Rd., Ottawa, ON K1H 8M5.**

CHAIRE D'UROLOGIE: ON – L'Université d'Ottawa ouvre un concours pour le poste de directeur de la division d'urologie, Université d'Ottawa, École de Médecine. Les candidat(e)s qualifié(e)s devront avoir un certificat du Collège royal des médecins et chirurgiens du Canada et être élégibles au permis d'exercer du Collège des médecins et chirurgiens de l'Ontario. Le(la) candidat(e) choisi(e) sera le(la) responsable de la coordination des programmes d'enseignement intégrés dans les hôpitaux affiliés, soit l'Hôpital Général d'Ottawa, l'Hôpital Civic d'Ottawa, et l'Hôpital pour enfants de l'est de l'Ontario. Le(la) candidat(e) choisi(e) aura aussi la responsabilité des programmes de formation au nivea prédiplomé et postdoctoral et du développement des programmes de recherche. Le(la) candidat(e) choisi(e) agira conjointement comme directeur(trice) de la division d'urologie dans l'un des hôpitaux affiliés. L'Université et les hôpitaux affilié offrent d'excellentes resources qui assurent une médecine de qualité et des programmes de formation bien structurés. L'Université d'Ottawa offre un salaire de base concurrentiel, ainsi que des conditions de travail et des avantages sociaux alléchants. L'Université a une politique d'égalité en matiére d'emploi. Selons les exigences d'Immigration Canada, cette annonce s'adresse d'abord aux citoyens canadiens et aux résidents permanents du Canada. Prière de faire parvenir votre curriculum vitae et la liste des références avant le 1 juin 1989 à l'attention de: **Gilles D. Hurteau, MD, Doyen, Ecole de médecine, Université d'Ottawa, 451, chemin Smyth, Ottawa, ON K1H 8M5.** –S89-16

VASCULAR SURGEON: ON – Applications are invited for a clinical position at the Ottawa Civic Hospital. Candidates must hold a certificate of special competence in vascular surgery (or equivalent) and have added qualifications in epidemiology/public health. Training in critical care is an asset. The closing date for applications is 30 days after publication of this advertisement. Applications, including curriculum vitae and names of three referees, should be submitted to: **C. Wm. Cole, MD, Division of Vascular Surgery, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, ON K1Y 4E9.** –S89-17

GENERAL SURGEON: SK – An opportunity exists for a general surgeon to join in busy practice of general surgery, university centre, western Canada. Please send CV to: **Box 726, Canadian Journal of Surgery, PO Box 8650, Ottawa, ON K1G 0G8.** –S89-01

ADVERTISERS' INDEX

For prescribing information see page 210 →

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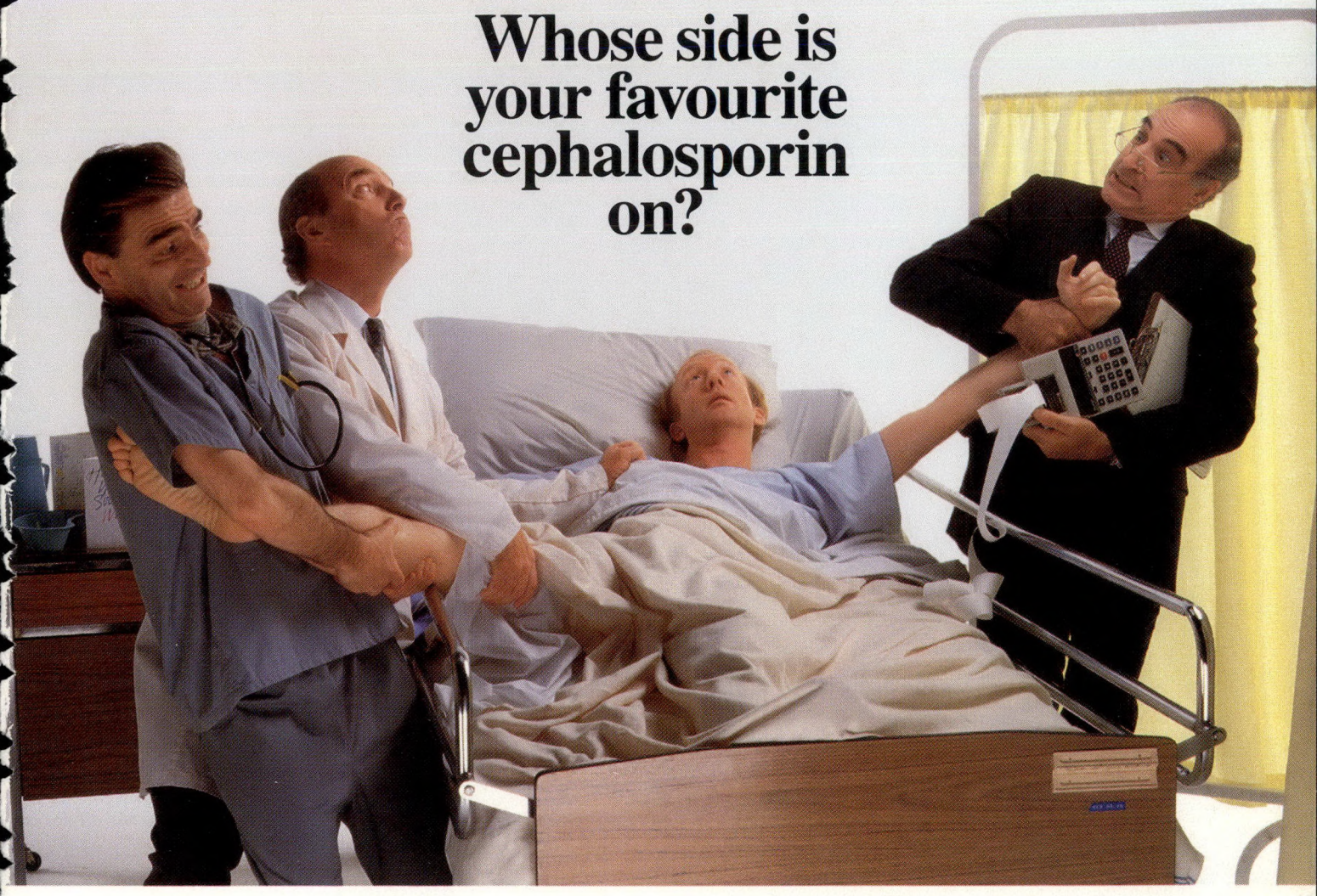

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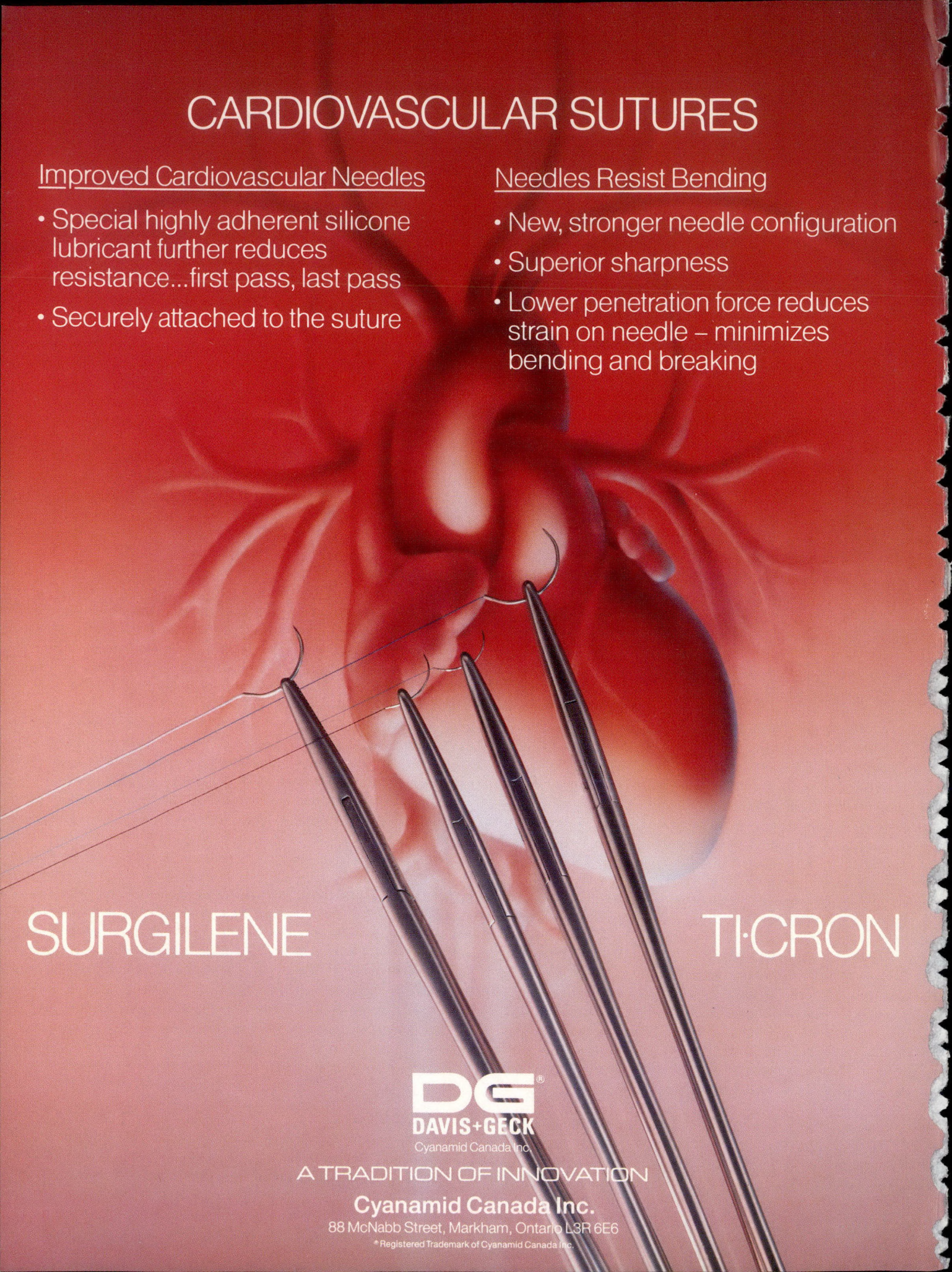

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