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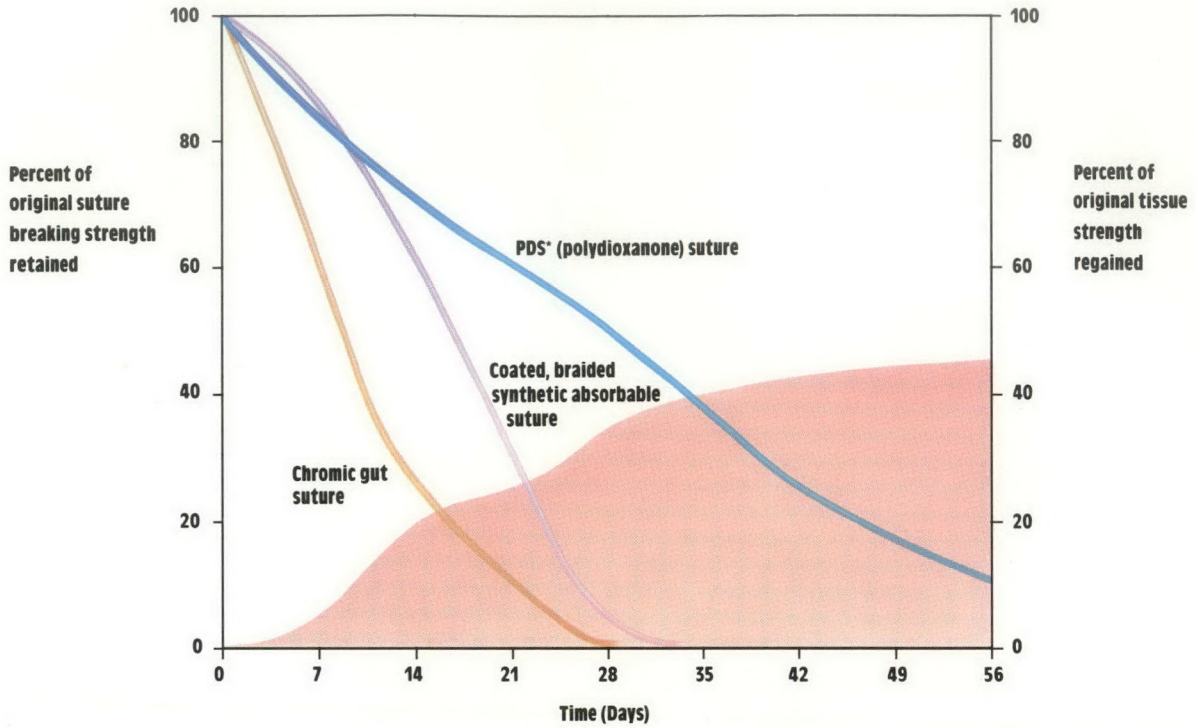
Volume 29, No. 4, July 1986

Gastric Ulcer
Microvascular Surgery
Intra-arterial Streptokinase

The Canadian Journal of Surgery

Le journal canadien de chirurgie

Holds till it heals.



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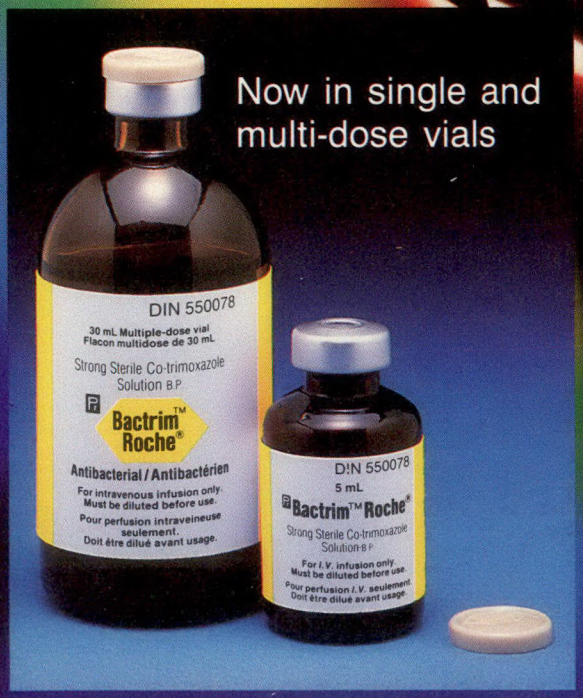

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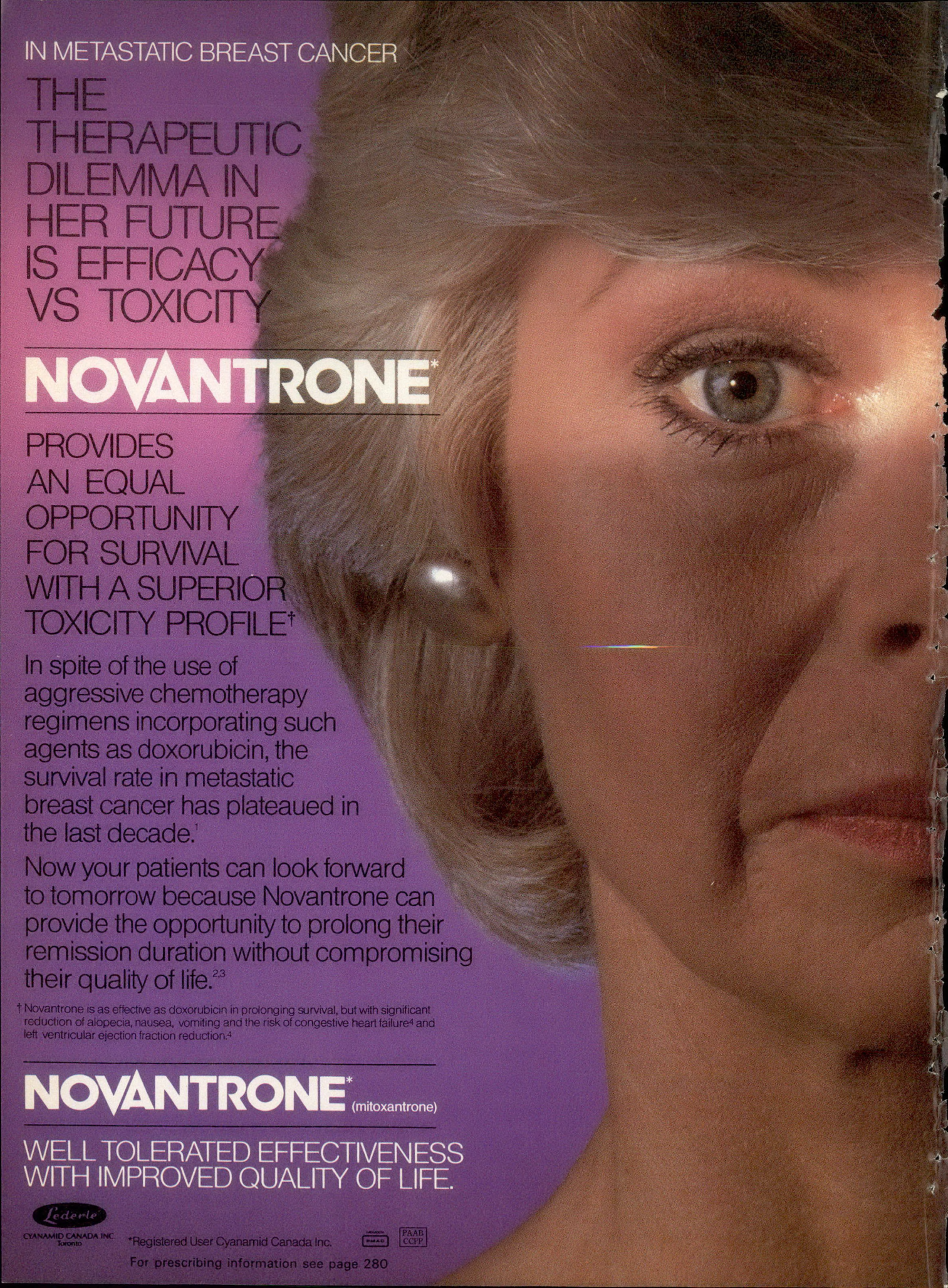

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QUILL ON SCALPEL

This section provides a medium through which Canadian surgeons can declare themselves, briefly and informally, on the day-to-day affairs of surgery.

Perspectives on Malignant Biliary Obstruction: Does the Surgeon Have a Role in Management?

Concepts of intervention for malignant biliary obstruction have altered substantially since the first reports of successful percutaneous drainage in 1978[1] and endoscopic drainage in 1979.[2] Management previously had been entirely operative with most treatment decisions being made by surgeons, who carried out palliative bypass in the majority of cases. However, current imaging techniques for obstructive jaundice often involve radiologists and gastroenterologists before the surgeon is consulted. In fact, the imaging requests may be followed directly by an interventional procedure that is considered definitive treatment by the operator.

This may be appropriate if all biliary strictures were considered to be incurable malignant lesions. However, most authorities accept that certain ampullary and bile-duct carcinomas are curable. Whether the same is considered true for pancreatic carcinoma is debatable. None the less, not all lesions obstructing the bile duct will prove to be of pancreatic origin, so consideration of surgical cure should not be withheld from patients when even slight hope of resectability exists.

The combination of cholangiography and sophisticated abdominal scanning techniques should allow biliary disease to be categorized, so that the surgeon, radiologist and gastroenterologist together could select the appropriate therapeutic technique. Advanced metastatic obstruction of the bile duct or primary hepatobiliary-pancreatic carcinoma with proven unresectable spread should be considered for nonoperative palliation. But a distal bile-duct stricture without any definition of the mass by scanning demands that resectability be verified by operation. Even hilar bile-duct lesions without a large mass effect or intrahepatic spread may be resectable, although not always curable.[3] I propose that, before any intervention, the mode of treatment should be decided upon jointly by staff from all disciplines involved, using the experience and expertise of all available specialists.

Discussion of the management of unresectable disease frequently compares the results of various forms of palliative intervention with those of operative bypass. Often the surgical statistics quoted are outdated and describe small numbers of cases; universally, the results from the surgical series selected are inferior to those of the palliative technique under consideration. Sarr and Cameron[4] reported the results of surgical palliation for pancreatic carcinoma collected between 1965 and 1982. Over 10 000 patients were treated by biliary–enteric bypass, with a mean survival of 5.5 months. Patients who did not undergo bypass survived 3.4 months after

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Detailed instructions to contributors, in English and French, appear on page 56 of the January 1986 issue.

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laparotomy alone — a result similar to those from many reports of nonoperative biliary drainage.[4] This historical baseline must be considered whenever results of intervention are debated.

The results of prospective randomized trials may be valuable to compare the quality and duration of palliation for unresectable disease. Such analysis offers an improvement over retrospective analysis of interventional palliation describing success in terms of radiologic illustrations or biochemical changes. Any trial must indicate success or failure in terms of restoration of normality, the severity and frequency of disabling morbidity, recurrence of presenting problems and length of survival. For comparative results to be meaningful, they must be categorized. Cholangiography and scanning will be valuable in this respect. However, pathologic features of the tumour may not be obtainable in all cases, and the biologic behavioural differences between bile-duct carcinoma and pancreatic carcinoma are enough to affect the evaluation of data from any sample size.

Nonoperative biliary drainage is associated with a lower morbidity and mortality than surgery in most reports from experienced units. This is particularly true for the procedure alone, considering the complexities associated with operation and anesthesia in patients with decompensated liver function and suppressed immune response. However, the 30-day death rate may be equal to or greater than that for operation when short-term complications of percutaneous and endoscopic stenting are included in the analysis.[5]

As Olak and associates report in this issue (pages 243 to 246, sepsis is extremely important whenever palliative bypass is not wholly internal. External cannulas are considered important for changing stents in the presence of infection. Indeed, the results justify the need. Similar requirements exist for endoscopic stenting due to infection and occlusion of the prosthesis. Surgically placed U tubes suffer a similar fate and require frequent changes. Surgically placed endoprostheses, free of external conduits, are rarely complicated by infection or occlusion.[6,7] This may also correlate with the increased luminal diameter of the stent sustaining improved bile flow.

No area has so long been the sacred ground of general surgery as has the biliary tract. Surgical competence in this region is rarely questioned of qualified specialists. Our results are so uniformly outstanding that we almost never audit our work and rarely publish the results of other-than-unusual cases or collected series from referral centres. However, be aware of intrusion from non-surgeons, who are capable of treating our diseases. They have little more than scopes, needles and catheters. They understand imaging as well or better than we do. They communicate with patients and referring colleagues as well or better than we do. Indeed, they may be as aggressive as we think we are! And they do audit their results and publish even small series of cases, creating awareness of the frontiers that have been opened in our field by non-surgeons.

We cannot all become endoscopists capable of interventional techniques, nor radiologists skilled in percutaneous therapy; however, we can evaluate our role in current-day management of disorders of the biliary tract, determine our place on the team that will be involved in investigation and treatment, upgrade our surgical skills and techniques, take part or direct audits of the therapies applied, and report results in print or presentation. The alternative does not bode well for general surgery.

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Modern Management of the Unruptured Tubal Pregnancy

Between 1970 and 1980 there was a threefold increase in the occurrence of ectopic pregnancy.[1] In 1883 Lawson Tait performed the first salpingectomy for this condition. After excision of the affected oviduct, the standard gynecologic practice for ectopic pregnancy, patients can be expected to conceive in 50% of cases, have a live birth in 34% and a repeat ectopic pregnancy in 16% of cases.[2] This traditional form of surgical management, while undoubtedly life-saving, does little to enhance the future fertility of women wishing to preserve their reproductive potential. During the past decade alternative, more conservative, methods of management have been explored with considerable success. Since little other than partial salpingectomy can be offered to the woman who has suffered catastrophic rupture of a tubal pregnancy, earlier diagnosis before rupture is the keystone of a more conservative approach.

The combination of acute clinical awareness of the condition, measurement of the circulating levels of the beta subunit of human chorionic gonadotropin[3] and ultrasonographic assessment of the pelvic organs in most cases will allow early diagnosis to be made. The woman with a short period of amenorrhea, pelvic pain and vaginal spotting, in whom an elevated level of beta human chorionic gonadotropin is detected may indeed suffer from this condition. By the 25th day after conception a gestational sac can be detected by ultrasonography within the uterine cavity. If no such sac is detected,

the patient should be considered to have an ectopic pregnancy until proven otherwise. The next logical investigation is laparoscopy. Of 165 patients examined laparoscopically by Samuelsson and Sjövall[4] and believed to have an ectopic pregnancy 164 did so and of 312 thought not to have ectopic pregnancy the diagnosis was correct in all but 6. Laparoscopy provides the opportunity to make a concrete diagnosis, to assess the status of the contralateral oviduct and, in many cases, to perform definitive conservative surgery. The use of laparoscopic electrosurgical methods will allow performance of linear salpingostomy or minimal segmental resection of the gestational sac.[5]

For the surgeon unfamiliar with laparoscopic surgical techniques, a simple alternative is to combine laparoscopy with mini-laparotomy. Such a procedure is feasible only in the slim patient in whom the uterus and affected oviduct are freely mobile. When a uterine cannula is placed in the cervix it is possible to manipulate the uterine fundus immediately beneath the anterior abdominal wall. A 1- to 2-cm suprapubic incision is all that is required to deliver the tube to the exterior where a conservative surgical approach can be undertaken.[6]

If formal laparotomy is undertaken the pregnancy can be milked from the tube if it is in the ampullary portion. The results have been less than satisfactory, with a repeat incidence of ectopic pregnancy of 21.4%.[7] The optimal approach would appear to be linear salpingostomy. Women whose incisions were permitted to heal by secondary intention have been shown by DeCherney and colleagues[8] to do better than those in whom primary closure was undertaken. Langer and colleagues[9] studied 54 patients in whom linear salpingostomy was performed 44 times and milking 13 times. Of 49 patients who wished to become pregnant, 71% experienced a live birth and there was an ectopic pregnancy rate of only 12%. Perhaps more impressive than the intrauterine pregnancy rate of 90% in patients with a healthy contralateral tube was the intrauterine pregnancy rate of 62.5% in patients in whom the contralateral tube was absent or damaged.

Undoubtedly these conservative approaches are more effective when microsurgical techniques are used. Such a statement may intimidate the practising surgeon who has not had special training in microsurgery, but there is nothing mystical about these procedures, relying as they do on the principles of magnification, pinpoint electrocautery and delicacy in tissue handling. Magnification for the conservative management of the tubal pregnancy is provided very adequately by opthalmologists' loupes which give a magnification of 4 × or 6 ×. Any solid-state electrocautery machine can be used in conjunction with a pinpoint electrocautery needle. Irrigation can be provided by a 20-ml syringe and an Angiocath. When salpingostomy is performed, a few fine, preferably 8-0, sutures at the angles of the incision will usually be all that is needed to secure hemostasis. Perhaps in the future ectopic pregnancy diagnosed early will no longer be treated surgically. A recent report[10] demonstrated that when six patients with unruptured ectopic pregnancies were treated with methotrexate and folic acid, all responded to one course of treatment and none required surgery. Hysterosalpingography performed 3 months after treatment revealed patent tubes and normal uterine anatomy. While such reports are preliminary and do not provide information about subsequent pregnancy and ectopic pregnancy rates, they do hold promise for noninvasive management.

Although in-vitro fertilization techniques may provide future hope for women who suffer from ectopic pregnancy, attempts at primary conservation add little to the operating time, do not involve expensive high-technology methods and appear to have a gratifying success rate with respect to live births. It should now be incumbent upon any surgeon involved with the gynecologic care of women to consider early diagnosis and conservation of the affected fallopian tube.

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CORRESPONDENCE

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

Campylobacter jejuni Associated With a Perirectal Abscess

To the editors.—Campylobacter jejuni is a slender, curved, S-shaped or spiral, motile, microaerophilic, gram-negative bacillus, positive for sodium hippurate hydrolysis.[1] Acute enteritis is the commonest clinical manifestation of infection due to this bacterium,[2] which may cause a variety of other intestinal disorders—toxic megacolon and colitis,[3] massive gastrointestinal hemorrhage,[4] cholecystitis[5] and pancreatitis.[6]

We report a case of *C. jejuni* isolated directly from a perirectal abscess, which we believe is the first such report.

Three weeks before being seen in the clinic, a 64-year-old woman experienced an episode of diarrhea (5 to 10 movements daily), associated with abdominal pain. The attack resolved spontaneously within a week. There was no fever, nausea, vomiting or hematochezia. There had been no recent exotic travel or consumption of unpasteurized dairy products or inadequately cooked meat.

Two weeks later, a gradually increasing painful mass developed in the right perianal area, unassociated with fever or chills. A right perirectal abscess was found and drained through an incision placed in the squamous epithelium of the right buttock after appropriate disinfection. Pus was sent to the microbiology laboratory. However, owing to a clerical error the specimen was labelled as "rectal swab" rather than "perirectal abscess", and was handled as a stool sample rather than an abscess. As such, cultures for anaerobes were not done. *Campylobacter jejuni* and *Citrobacter freundii* were isolated from the specimen.

Most perirectal abscesses are thought to arise in the 6 to 10 anal glands that empty into the anal canal at the dentate margin. The infection begins in the plane between the internal (visceral) and the external (somatic) sphincters. From there the infection progresses caudally to form the common low variety of perianal abscess that accounts for about 80% of anorectal suppuration.

The bacteriologic findings in perirectal abscess have been well described; they usually represent mixed infections involving anaerobes, particularly *Bacteroides fragilis* and gram-negative enteric bacilli.[7] Our patient is the first in whom *C. jejuni* has been isolated from an abscess at this site. One may speculate that the episode of self-limited enteritis was caused by *C. jejuni* and was subsequently complicated by an abscess due to this organism in proximity to the gastrointestinal tract. Similar manifestations (perineal, perirectal abscesses) are well-known in relationship to *Salmonella* infections.[8]

It is recommended that any patient with a perirectal abscess who has suffered enteritis in the preceding few weeks and requires incision and drainage should have samples of pus sent to the microbiology laboratory. The laboratory should be asked to culture not only aerobes and anaerobes, but also *Campylobacter* which requires specific media and culture conditions for isolation.[1]

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Tube Cecostomy

To the editors.—To evaluate the role of tube cecostomy, one must consider the purpose of the procedure, its effectiveness and its morbidity.

The purpose of tube cecostomy is to decompress the colon. Decompression involves the release of gas, liquid and solid material. Rosenberg and Gordon in the January 1986 issue of this journal (pages 38 to 40) showed that tube cecostomy is not reliably effective in achieving that goal. Frequent and unavoidable tube obstruction is the limiting factor in this procedure. A mucosa-to-skin cecostomy without a tube may reduce the incidence of obstruction. However, the stoma may be small, diversion incomplete and a second operation required for closure.

Rosenberg and Gordon outlined the morbidity associated with tube cecostomy, further emphasizing the disadvantages of this procedure.

Are there any indications for this procedure, which is, at best, partially decompressing? The intraluminal stapler has made it possible to create more secure anastomoses in the pelvis and has reduced the need for proximal diversion of the fecal stream. If such diversion is deemed necessary, a loop transverse colostomy or a loop ileostomy will more completely divert gas, liquid and solid material than tube cecostomy. The Division of Colon and Rectal Surgery at the University of Minnesota has used proximal diversion of left-sided colonic anastomoses in only 13% of 2537 cases. A cecostomy in which the mucosa was sutured to the skin was

used once with good anastomotic healing; however, the cecostomy continued to drain small amounts of stool and was still not closed 2 years after surgery.

Cecal volvulus requires a procedure that will release gas from the cecum and prevent recurrent volvulus. Tube cecostomy is better suited to this role, but again the incidence of tube obstruction limits the value of this procedure. Ileocecal resection is a safe and more reliable alternative.

Pseudo-obstruction of the colon requires temporary gas decompression of the cecum. If colonoscopic decompression has failed, a tube cecostomy may be considered. However, a mucosa-to-skin cecostomy is more reliable.

In summary, tube cecostomy is not a reliable means of diversion or decompression for protecting distal anastomoses. Cecal volvulus is best managed by resection and primary anastomosis. Tube cecostomy or a mucosa-to-skin cecostomy may still have a role in the management of pseudo-obstruction of the colon unresponsive to colonoscopic decompression. Currently there are no other indications for the use of tube cecostomy.

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Organization of Trauma Care

To the editors.—Although you are to be commended for an excellent overview of trauma care systems in Canada (vol. 28, no. 6, November 1985), I would like to update you on progress being made in Ontario. Presently, we have one central air ambulance dispatch for the entire province and central land ambulance dispatch for all the major urban and regional centres.

With respect to the air ambulance, in Ontario, Bandage 1 helicopter which operates out of Toronto and covers central Ontario has had paramedical staff for 7 years. In addition, advanced life support is being introduced in the near future to the two helicopters and two small jets that operate as dedicated air ambulances in Northern Ontario.

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Management of Breast Fibroadenoma in Women Under 25 Years of Age

To the editors.—Deschênes and associates (*Can J Surg* 1985; 28: 372–374) advocate delayed excision of breast fibroadenomas for women under 25 years of age with a cytologically confirmed tumour on the grounds that the risk of breast cancer is small and spontaneous regression may occur. In a retrospective study[1] of 134 patients with a clinical diagnosis of fibroadenoma, cancer was found in 8. One of these patients was only 26 years old. Fine-needle aspiration biopsy has a sensitivity of over 95% in the diagnosis of suspected malignant breast masses,[2] but a negative result is of no value. In two out of eight patients with a clinical diagnosis of fibroadenoma who later were found to have cancer, fine-needle aspiration cytology gave negative results.[1]

The extent to which fibroadenomas may show spontaneous regression is uncertain. In one report[3] only 2 of 17 fibroadenomas observed for varying periods regressed. The standard treatment of fibroadenoma should, therefore, remain surgical excision[1] since it is both diagnostic and therapeutic.

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2. DIXON JM, LAMB J, ANDERSON TJ: Fine needle aspiration of the breast: importance of the operator (C). *Lancet* 1983; 2: 564
3. FURNIVAL CM, IRVWIN JRM, GRAY GM: Breast disease in young women. When is biopsy indicated? *Med J Aust* 1983; 20: 167–169

To the editors.—We fully agree with Kapoor and Sharma that excisional biopsy is the standard management of women with a presumptive clinical and cytologic diagnosis of fibroadenoma. Like Haagensen,[1] however, we see no point in rushing patients under 25 years of age to the operating room. The risk of a malignant condition is, indeed, minimal at that age. Among our 762 patients with histologically confirmed fibroadenoma, studied in the last 8 years, 158 (20.7%) were in the 20- to 24-year age group and 85 (11.2%) were under 20 years of age, the youngest being 15 years old. On the other hand, in Haagensen's series of 6000 patients with carcinoma of the breast[1] and in our series of 1564 cases, there was no woman in her teens and there were, respectively, 9 (0.15%) and 3 (0.19%) patients aged 20 to 24 years. In these 12 young patients with breast cancer, clinical findings were not suggestive of a fibroadenoma.

Prompt surgery is justified for young women with a presumptive diagnosis of fibroadenoma who mention a rapidly growing lump, have a tumour measuring more than 15 to 20 mm in diameter or seem anxious. Otherwise, we recommend an excisional biopsy in the next few months at the patient's convenience. Occasionally, at re-examination, the tumour has vanished. If a biopsy is not performed, it is practically impossible to know whether the lump was in fact a fibroadenoma, a small cyst depleted by the fine needle of the aspiration biopsy or a nodule associated with premenstrual changes in the breast.[2]

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BOOKS RECEIVED

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

Acute Peripheral Vascular Surgery. Michael Staudacher. 165 pp. Illust. Springer-Verlag New York, Inc., New York, 1985. $38.50 (US). ISBN 0-387-81874-X.

Atlas of Skeletal Dysplasias. Ruth Wynne-Davies, Christine M. Hall and A. Graham Apley. 646 pp. Illust. Churchill Livingstone, Edinburgh; Academic Press Canada, Don Mills, Ont., 1985. $230.95. ISBN 0-443-03047-2.

Colorectal Tumors. Edited by Oliver H. Beahrs, George A. Higgins and Jacob J. Weinstein. 334 pp. Illust. J.B. Lippincott Company, Philadelphia, 1986. $57.50 (US). ISBN 0-397-50677-5.

Corrective Osteotomies of the Lower Extremity After Trauma. Edited by G. Hierholzer and K.B. Müller. 407 pp. Illust. Springer-Verlag New York, Inc., New York, 1985. $75. (US), ISBN 0-387-15879-0.

Diabetic Renal–Retinal Syndrome. Volume 3. Therapy. Edited by Eli A. Friedman and Francis A. L'Esperance, Jr. 572 pp. Illust. Grune & Stratton, Inc., Orlando, Fla.; Academic Press Canada, Don Mills, Ont., 1986. $130.25. ISBN 0-8089-1741-2.

continued on page 242

SURGEONS' UPDATE

What's new in surgery is the subject of this column. The short items are designed to let readers know who's doing what and why. Surgeons are interested in what other surgeons are doing in research, education, practice and administration. Surgery is a vibrant specialty, and, as its practitioners, you must be the source as well as the readers of this column.

Heart Transplants Likely to Quadruple in Canada by 1990

"Between ages 10 and 55 years, about 1500 to 2000 people in Canada each year could benefit from heart transplantation; if you extend the age limit to 65, the number is probably doubled," says the man heading the newest heart-transplant program in the country.

Dennis Modry, FRCSC, who spent 3 years at Stanford and was chief of the transplant service in his last year there, received approval from the Alberta government on May 1 this year for a program at the University of Alberta Hospital in Edmonton, giving the western provinces their first centre for heart and heart–lung transplants. The approval follows a pilot program in which Modry's team performed three heart transplants — the first one on July 28, 1985 — and then analysed the costs and results of the care both in and outside the hospital.

Within 4 years, Modry expects his and other Canadian centres each to be performing about 50 heart transplants annually. "The goal for 1990 is to do about 500 transplants across the country in 10 or so centres; the centres performing heart–lung transplants may each do another 5 or 10 of those. That's a realistic number to aim for given the status of available donors. If legislation is enacted to make it incumbent upon physicians to approach donor families, then the transplant teams could conceivably handle about two-thirds of the people who can benefit from the procedure.

"In Edmonton, we have now accepted seven individuals as recipients for heart transplants but there are hundreds that have been referred from British Columbia, Alberta and Saskatchewan. There is talk of another two western centres — one in Vancouver — that should come on stream in a couple of years and one in Winnipeg. Most centres begin with heart transplantation and move into the more difficult heart–lung procedure. For our program, the next transplant could be a heart–lung operation as far as I'm concerned since I've done several at Stanford and a great number in the lab.

"Since we are just getting started in transplantation we haven't assessed the wait list. In future, we will probably have actively selected 12 to 15 people at any one time, although there may be anywhere from 50 to 75 who are waiting to get on the active list."

At present, like Modry's group, most of the other centres are just gearing up, averaging fewer than 10 each in the past year. Besides the group in Edmonton, teams at four hospitals in Montreal, two in Toronto, one in London and one in Ottawa are performing heart or heart–lung transplants.

As the procedures are performed only on individuals with "end-stage" disease, the operation's ability to extend life has not been debated since survivors undoubtedly live longer than they would have without the transplant and success rates approach 90% in most centres.

Ottawa Team Opts for Artificial Heart

At the success rates typical of heart transplant programs, the risk of imminent death for recipients is much greater before than after transplantation — a reality that has prompted cardiac transplant teams not only to step up the numbers of operations but to seek reliable means of temporary support until a human heart becomes available. So it was that in May, the University of Ottawa Heart Institute — or rather team leader Wilbert Keon, FRCSC, coordinator Arvind Koshal, FRCSC, Alan Menkis, clinical and research fellow, and resident Ed Farrell — became the first in Canada to test an artificial heart as a means to bridge the time between heart failure and receipt of a suitable donor heart.

Menkis has submitted for publication a report of the events leading up to and following the use of the Jarvik 7-70 in Noella Leclair but briefly reviewed the event: "The patient was a 41-year-old mother of one who was asymptomatic before the initial infarct. During the next week the infarct extended to cover most of her left ventricle, and despite all of the usual and dramatic things that cardiologists and cardiac surgeons do, including the use of streptokinin, intra-aortic balloon pumping and subsequent double bypass, she couldn't come off bypass. By the time we put in the artificial heart she was effectively dead." The decision proved timely and, despite some bleeding, she was "in good shape when a donor became available". Thus, the first recipient of an artificial heart in Canada became the 12th to receive a human heart at the institute, which began its program 2 years ago. (True to the statistics elsewhere, one patient in the series died, 5 weeks after transplantation.)

As might be expected, the technique for inserting the air-driven pump made of plastic and metal differs substantially from that for a human heart, so last year the team spent time learning the procedure with the heart's developer in Salt Lake City.

The Jarvik heart has now been used at least 12 times to maintain individuals awaiting human hearts, and only two patients have reportedly died while it was

Contributions to this column are welcome. Please send your material to: Mrs. Amy Chouinard, *Canadian Journal of Surgery*, PO Box 8650, Ottawa, Ont. K1G 0G8.

inserted. It has not been compared with other means of temporary support but was the method with which the Ottawa team felt most comfortable.

Methods of bridging will be used increasingly often, not only for patients like Leclair who deteriorate rapidly, but also for those who become victims of the competition for organs. At present, only about 15% of organs that could be used for transplantation are being donated, and the frustrating part, says Menkis, is "Every institution in Canada is capable of contributing donors. Whether it is capable of retrieving the organs is irrelevant, since the MORE (Multiple Organ Retrieval, Toronto) system will arrange for someone to come to the institution. A very small hospital can contribute organs if it has the intensive care facilities to keep someone who is brain dead physiologically going.

"When you have a recipient or donor, you call MORE or NATCO (North American Transplant Coordinating Agency), and the staff there make a preliminary match by blood type, size and age of the individuals. An urgency or status-nine list is reserved for patients in imminent danger of dying."

Leclair was put on the list. The heart that she eventually received was from a 44-year-old Montreal man killed in a car accident near London, Ont.

At one time, a heart older than 35 years wouldn't have been considered because of the prevalence of heart disease in North America, but, says Menkis, "Generally all the programs are relaxing their criteria somewhat, using chronologically older donors and recipients. We do an angiogram to confirm there is no coronary artery disease in older donors...the healthy heart of a 40-year-old is better than the near-dead heart of the recipient."

London Multiorgan Service to Perform 200 Transplants

Calvin Stiller, FRCPC, chief of the multiorgan transplant service at University Hospital, London, Ont., reports that the cardiac transplant team there performed 19 heart transplants in the first quarter of this year and by the end of May had done more than 70.

"Although, like most transplant programs, we initially were quite restrictive about recipients, we are now taking patients on the basis of their need. We have performed heart transplants in 15 older than 50 years and 10 older than 55 years. The current success rate is over 80% for the entire program."

Stiller prefers to discuss the complete multiorgan service. The statistics are impressive, with similar success rates across the board for kidney, liver and heart.

The teams in the service expect to perform transplants at the rate of about two kidneys, one heart and one liver each week this year.

Says Stiller, "About four of every five transplant recipients will regain their preillness health at a cost to society of about $40 000 to $50 000 for every heart and liver transplant and something in the region of $25 000 for every kidney. Each of the clinical programs is preceded by intensive work in the laboratory. For instance, right now transplant programs for intestines, limbs and islets are in the preparatory period, with clinical applications expected in the next 2 to 3 years. A facility is now under construction to house the whole program; a 12-bed unit is being built and will open in December, the focus being detection and management of rejection."

Montreal MD Recalls Events Leading to His Heart Transplant a Year Ago

"I had everything to contraindicate transplantation," says Samir Chebeir, FRCSC, who at 49 years was still within the criteria for age, but was suffering from pulmonary infection, renal insufficiency and hypotension, as well as having numerous rib fractures and a swollen foot from misguided medical care he had received days before in the Azores Islands.

Albert Guerraty, FRCSC, head of the heart-transplant team at the Royal Victoria Hospital in Montreal, had to be pushed to perform the operation according to Chebeir: "I was in very bad shape; he told everyone I was going to die, but he operated on me April 29, 1985. After the transplant I was in a coma for 3 days, I had to have dialysis and I had a gastric hemorrhage."

When it had all begun 1 month earlier, Chebeir and his wife were en route to Portugal for a holiday. As the plane stopped to refuel in the Azores Islands, Chebeir, who had no history of heart disease and was a hard-working obstetrician-gynecologist, experienced a sharp, unmistakable stab.

He called for oxygen, and when no one responded he fumbled to find the plane's canister. It was empty, but a flight attendant noticed the commotion and began to chastise him before realizing his distress. A fellow traveller — a doctor from Toronto — took his pulse, confirmed arrhythmia and administered lidocaine hydrochloride and called an ambulance.

The first hospital sent him to a second where he was admitted. As he entered, he moved backward in time — to the days when defibrillators caused every muscle in the body to contract, when anesthetics were not offered and no equipment except an electrocardiograph was used for investigations. He watched his electrocardiogram charting a series of arrhythmias; he was given a pacemaker. He continually asked to be allowed to return to Canada for treatment.

He had no phone in his room, and the receptionists at the hospital spoke only Portuguese so relayed no messages to him. His request for assistance in reaching specialists in Montreal was denied. His wife succeeded in arranging for colleagues at Hôtel-Dieu — a cardiologist and cardiac surgeon — to obtain whatever they needed in the way of equipment and medications and to rent a jet from New Jersey. They arrived in the Azores to oversee his flight home.

Back in Montreal, the investigations began. Besides the ischemic cardiomyopathy, he had pulmonary infection, hypotension, renal insufficiency, an inflamed foot, and every day he required either cardiac massage or defibrillation, the cardiac arrests numbering more than 100 before he underwent transplantation.

Chebeir has had no episodes of rejection; he takes cyclosporine (150 mg twice a day) and cortisone (10 mg daily). Periodically he has also needed captopril for renal hypertension related to the long-term use of cyclosporine. His serum creatinine levels are elevated (between 159 and 194 μmol/L) and although he is prepared to decrease his intake of cyclosporine, he refuses to consider a regimen without the drug. "If I switch now to Imuran (azathioprine), the chances of rejection, I think, are high, and it's impossible to know beforehand. I prefer to diminish the dosage of cyclosporine."

By radioimmunoassay, the levels of cyclosporine in his blood are within the range considered suitable for maintenance — between 90 ng and 150 ng/ml.

Chebeir is one of 19 who have received new hearts at the Royal Victoria Hospital. All but one are still alive and have Guerraty and his team to thank. To show his gratitude, Chebeir has been instrumental in obtaining support from the private sector for the program. Lloyd MacLean, FRCSC, surgeon-in-chief, noted that Chebeir has been able to put the services of a Lear jet at the disposal of the transplantation unit when a donor heart needs to be picked up, even from as far away as South Carolina.

Says Chebeir, "The cardiac team at the Royal Victoria is very capable and could do even more than they are doing now if they had some help. The government has not provided funds and the conditions at the hospital are not what one would

expect for sophisticated surgery. The hospital doesn't have anything — I had to bring a chair from my home for my room.

"Competition with other hospitals for funds has been detrimental, and my aim is to help establish a foundation for heart transplantation so that everyone who needs a transplant can have one."

In the meantime, Chebeir has done much to facilitate organ procurement and he would like to see the government do more. "At least three or four are awaiting heart–lung transplants at the Royal Victoria and another six are waiting for hearts. In April, the shortage was serious for many centres. What we need to do is to persuade the government to pass a law similar to the one in France, number 761181 du Conseil d'état." This law assumes that a person is willing to donate organs unless he or she officially opts out.

Few surgeons would disagree with Chebeir that the pool of donors has to be extended, but the methods for doing so are widely debated.

Heart–Lung Transplants in Toronto Began as Treatment for End-Stage Lung Disease

The Toronto team performing heart–lung transplants, unlike the others in Canada, began the operation as an extension of their program to deal with end-stage lung disease.

Joel Cooper, FRCSC, who heads the program as part of the division of thoracic surgery at the University of Toronto, explains: "There are two components of the program — single-lung and heart–lung transplantations. The former is unique in that we have the only successes in the world after about 45 unsuccessful tries over the past 20 years. We've done single-lung transplants in five patients with pulmonary fibrosis, with four long-term successes. The first was in November 1983, and that recipient is now 61 years old, leading a normal life. The second was a woman who's now touring Germany; she was confined to a wheelchair before the operation. All the survivors returned to work within 3 months.

"However, the heart–lung operation or — as we refer to it — the lung–heart operation is used in most places in the world for an individual whose heart has failed in association with some narrowing of the blood vessels of the lung. We started using the operation because there are some people with lung failure for whom a single-lung operation is not suitable, for example, when the heart fails because of lung disease or when the patient has a condition in which one needs to take out both lungs, such as cystic fibrosis or emphysema. At the moment, the only way we can replace both lungs is to include the heart, although we are working on an operation for just the lungs.

"We have performed five heart–lung transplants, with four survivors. One of the survivors has now — a year later — died, probably as a result of chronic rejection. All the others are doing well. One was a gal from Chicago; another much-publicized case was a woman from Quebec — Diane Hebert. She had been down to Stanford for a couple of years and had come here to die. One was a chap from Calgary who had a congenital immune deficiency — agammaglobulinemia.

"At first I thought it was insane to consider a transplant for him. His defect meant he wasn't making B-cell antibodies to protect him against bacterial infection. To take someone like that and further suppress the immune system — do a T-cell immunosuppression to protect against rejection — I thought would render him hopelessly vulnerable. What I found out was that gammaglobulin can now be injected intravenously once a month to keep this type of individual immune competent. That treatment wasn't available before and the repeated infections destroyed his lungs.

"It's only one case so all I can tell you is that he probably had fewer problems with rejection than did anyone else, although some of the other recipients had only minimal rejection.

"For all our heart–lung transplant recipients, we use primarily cyclosporine for immunosuppression; after the first 3 weeks we also use prednisone — not before, because we feel it interferes with wound healing. We use azathioprine, and in the early days we sometimes use antilymphocyte globulin."

AMY CHOUINARD

SESAP V Question

Item 44

Which of the following statements about operative management of patients with unresectable carcinoma of the pancreas is TRUE?

(A) Gastrojejunostomy should be performed only if duodenal obstruction is already present

(B) Cholecystojejunostomy will reliably decompress the biliary tree if the gallbladder is distended

(C) Choledochoenteric anastomosis should be performed if the tumor encroaches on the cystic duct

(D) Placement of a hepatic U tube can provide excellent palliation if this procedure can technically be performed

(E) Routine drainage of the obstructed pancreatic duct is usually recommended

For the critique of Item 44 see page 286.

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Surgical Management of Gastric Ulcer

The charts of 139 patients operated on for benign gastric ulcer between 1976 and 1980 were reviewed. Indications for surgery included failure of medical management, bleeding, perforation and inability to differentiate benign from malignant disease. Surgical management included hemigastrectomy 29%, vagotomy with antrectomy 27%, vagotomy with pyloroplasty 13%, wedge resection 7% and highly selective vagotomy 4%. Eighty-four patients (60%) were available for a minimum 4-year follow-up. Recurrence rates were highest in those treated by highly selective vagotomy (33%) and wedge resection (30%). The overall death rate was 4.3%, and 70% of the patients were classified as Visick grades I or II (no or minimal symptoms).

Of the 30 patients with acute perforation, 21 were treated by omental patching; 1 died and 3 had recurrent ulcer. Of six patients treated by vagotomy with antrectomy, there were no deaths and no recurrences.

The authors conclude that lesser procedures are associated with an unacceptable recurrence rate and that gastric resection is the procedure of choice for both elective and emergency management of gastric ulcer.

On a étudié les dossiers médicaux de 139 patients qui ont été opérés pour un ulcère gastrique bénin entre 1976 et 1980. Parmi les indications chirurgicales, on notait l'échec du traitement médical, des saignements, une perforation et l'impossibilité de différencier l'ulcère bénin d'un cancer. Les techniques chirurgicales comprenaient 29% d'hémigastrectomies, 27% de vagotomies avec antrectomies, 13% de vagotomies avec pyloroplasties, 7% de résections cunéiformes et 4% de vagotomies hypersélectives. Quatre-vingt-quatre patients (60%) ont pu se prêter pendant un minimum de 4 ans a des examens de surveillance. Les plus hauts taux de rechute ont été observés chez les patients traités par vagotomie hypersélective (33%) et par résection cunéiforme (30%). La mortalité a été de 4.3%, et 70% des patients ont été cotés I ou II à la classification de Visick (absence de symptômes ou symptômes minimes).

Des 30 patients en perforation aiguë, 21 ont été traités par pose d'une plaque d'épiploon; 1 est décédé et 3 ont eu une rechute ulcéreuse. Il n'y a eu ni décès ni récidive chez les six patients traités par vagotomie et antrectomie.

Les auteurs concluent que les interventions limitées sont entachées d'un taux de rechute inacceptable et que la résection gastrique représente l'intervention de premier choix dans le traitement d'urgence ou différé de l'ulcère gastrique.

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Presented at the 8th annual meeting of the Canadian Association of General Surgeons held in conjunction with the 54th annual meeting of the Royal College of Physicians and Surgeons of Canada, Vancouver, BC, Sept. 10, 1985

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Peptic ulceration of the stomach has a number of characteristics in common with duodenal ulcer, especially when the distal antrum and pyloric region are involved.[1] However, ulceration of the body of the stomach remains distinct in its pathogenesis, the population at risk and potential for complications. Unlike duodenal ulcer, a major priority in the management of gastric ulcer is the early detection of a possible malignant lesion. Despite these differences, the surgical management of gastric ulcer is often based on the principles underlying duodenal ulcer, resulting in an inappropriately high incidence of recurrence and morbidity.[2–4] In an effort to define the features of gastric ulcer that demand separate consideration in surgical management, we undertook to review a series of patients treated at our institution.

Patients and Methods

The charts of all patients operated on for gastric ulcer at the major Dalhousie University teaching hospitals between 1974 and 1980 were reviewed. Ulceration was confirmed radiologically, endoscopically or by pathological study. Patients with coexisting duodenal ulcer were excluded, as were those with superficial erosions, gastritis or malignant gastric ulceration.

Follow-up information was obtained by questionnaire and by a review of hospital admissions after the ulcer surgery. Particular attention was paid to ulcer recurrence and postoperative syndromes.

A modified Visick classification was used to grade postoperative results, as follows: Visick I — no symptoms, Visick II — minimal symptoms, Visick III — severe symptoms controlled by medication and Visick IV — uncontrolled symptoms.

Findings

There were 139 patients (82 men, 57 women), with a mean age of 57 years. A minimum 4-year follow-up was possible

in 84 (60%). With respect to the surgical procedures performed, patient availability for re-evaluation was as follows: gastric resection 49%, vagotomy and antrectomy 58%, vagotomy and pyloroplasty 100%, wedge resection 56% and highly selective vagotomy 100%. Within the series, seven (5%) patients had previously undergone a Nissen fundoplication for gastroesophageal reflux.

Diagnosis

Endoscopy, the most common means of diagnosis, was used in 81 (58%) patients and correctly localized the ulcer in 73. As expected, those presenting with acute perforation were not subjected to endoscopy preoperatively. In 8 of the 81 patients the ulcer was not visualized endoscopically but was found at laparotomy. Biopsy and cytologic specimens were obtained through the endoscope in only 29 patients. Despite this, only 2 of the 139 patients were subsequently found to have underlying malignant disease.

Upper gastrointestinal series was used to identify the ulcer in 74 (53%) patients; the remainder were located at laparotomy. Acid secretory studies were carried out preoperatively in six patients, and, of these, acid secretion was normal in five patients and below normal in one.

The ulcer was located in the body of the stomach, along its lesser curvature, in 64 patients (46%). Of these, eight had ulcers in close proximity to the cardia. Fifty ulcers (36%) were in the prepyloric area and 17 (12%) arose from the gastric antrum.

Operative Procedures

The indications for operation and the surgical procedures performed are set forth in Tables I and II. The lowest recurrence rates followed gastric resection with or without truncal vagotomy.

Acute upper gastrointestinal bleeding was the indication for surgery in 32 (23%) patients. In three the bleeding point was simply oversewn because other risk factors were present, and in two of these the bleeding recurred immediately after operation, necessitating reoperation that resulted in the death of one patient. Six patients underwent vagotomy and pyloroplasty, two with concurrent wedge resection of the ulcer. Three patients underwent wedge resection alone. One patient, subjected to vagotomy and pyloroplasty, had recurrent bleeding postoperatively and required reoperation. No episodes of bleeding postoperatively were documented in 11 patients who had gastric resection or in 9 subjected to resection with truncal vagotomy. Surgery for bleeding gastric ulcer was followed by substantial morbidity. Wound complications occurred in 13 (41%) patients and 7 (22%) patients had respiratory complications. Overall, the postoperative death rate was 13%.

Thirty patients required surgery for acutely perforated gastric ulcer. Only 11 (37%) of them had a history of ulcer disease and 13 (43%) were poor surgical risks, because of advanced age, concurrent medical illness and delay before surgery. Free air was visible on abdominal films in only 52% of those in whom the study was carried out. The perforation was in the distal stomach and prepyloric area in 20 (67%) patients. Of 14 patients in whom specimens of peritoneal fluid were submitted for bacteriologic culture at the time of surgery, only 3 demonstrated substantial growth, consisting mainly of enteric organisms. A patch of omentum was used to seal the perforation in 21 patients, most of whom were poor surgical risks or had extensive peritoneal contamination. Biopsies of the ulcer were done in 12 of these and 3 suffered recurrent ulceration. One patient died shortly after operation. Truncal vagotomy and distal gastric resection to include the perforation was carried out in six patients, with no deaths and no recurrences.

Postoperative morbidity following surgery for perforation was again mainly in the form of respiratory (20%) and wound complications (13%). The overall death rate was 3%.

Overall Mortality and Morbidity

In the early postoperative period, six (4.3%) patients died. Acute bleeding was the indication for surgery in four of these, and in another acute perforation.

Wound complications were the most common source of morbidity postoperatively, occurring in 23 (17%) patients. These were followed by respiratory tract complications, with significant atelectasis and pneumonia occurring in 20 (14%) patients. Cardiovascular complications occurred in two patients and two experienced delayed gastric emptying in the early postoperative period.

Of the 84 patients available for follow-up, long-term morbidity was minimal, with 57% rated as Visick I and 13% as Visick II. Symptoms suggestive of the dumping syndrome occurred in five patients (6%), diarrhea in four (5%) and alkaline reflux gastritis in two (2%). Of these 11 patients with post-gastrectomy syndromes, truncal vagotomy had been carried out in 9 (82%).

Discussion

While the pathogenesis of gastric ulcer remains unknown, some accept that the basic defect is a deficiency in mucosal protective factors to the secretion of acid and pepsin. Davenport[5] and Du Plessis[6] suggested that ulceration results from duodenal alkaline reflux, with destruction of the gastric mucosal barrier and cellular destruction mediated by back diffusion of luminal acid. Thus, one would expect ulcer recurrence to be a common phenomenon following gastric resection. However, as in our series, recurrence rates have consistently been less than 5% when gastric ulcer is managed by resection.[7,8] Oi and colleagues[9] suggested that the tendency for gastric ulcer to involve the lesser curvature near the incisura angularis can be explained by the presence of a congenital point of least resistance where parietal cell mucosa borders on antral mucosa. The failure of wedge resection of the ulcer to prevent recurrence, as in our series, suggests that other factors are involved. Of interest in our series, was the association between gastric ulcer and previous Nissen fundoplication, an association already described.[10,11] Alkaline reflux into the stomach and esophagus and altered gastric emptying with hypergastrinemia have been proposed as possible contributory factors but are unproven.

Unlike duodenal ulcer in which the risk of underlying malignant disease is minimal, as many as 10% of gastric ulcers are ulcerating carcinomas.[12] This emphasizes the importance of endoscopic examination with tissue sampling in all patients whose gastric ulcer fails to heal rapidly with medical management or who demonstrate clinical features suggestive of malignant disease.

If endoscopy cannot be carried out preoperatively, as in acute perforation, gastric resection allows sampling of adequate tissue to exclude the presence of a malignant lesion. When resection is contraindicated, full-thickness biopsy specimens of the ulcer margins should be obtained before resorting to a lesser procedure, such as omental patching. The

Table I—Indications for Operation

Indication	% of patients
Intractability	37
Bleeding	23
Perforation	22
Possible malignant disease	14
Obstruction	3
Penetration	1

Table II—Procedures Performed and Postoperative Recurrences

Procedure	% recurrence
Vagotomy and antrectomy	0
Resection	5
Vagotomy and pyloroplasty	11
Wedge resection	30
Highly selective vagotomy	33

failure of endoscopy to detect the ulcer preoperatively in 10% of our cases is possibly related to those emergency situations with bleeding. It also suggests the presence of a blind spot in the stomach, especially on the lesser curvature, that should be carefully evaluated during endoscopic examination.

The high incidence of wound complications in our series underscores the need for perioperative antibiotic prophylaxis and peritoneal lavage in the management of gastric ulcer, especially in bleeding gastric ulcers in which the protective action of luminal acid is negated by the buffering effects of blood. During the period of our study, antibiotic prophylaxis and irrigation were not in widespread use.

Gastric resection, including the ulcer crater, appears to be the procedure of choice in the elective management of uncomplicated gastric ulcer. Recurrence rates of less than 5% have consistently been reported with acceptable postoperative morbidity and death rates.[7,8] Addition of a truncal vagotomy is indicated by the presence of a coexisting duodenal ulcer, the location of the ulcer in the prepyloric antrum or by preoperative acid studies suggesting hypersecretion. Vagotomy is not required for the treatment of proximal gastric ulcers or in patients with hyposecretion, as it can itself cause additional operative and postoperative problems.

Truncal vagotomy and pyloroplasty, when used to treat gastric ulcer is associated with recurrence rates higher than those seen when the procedure is used for duodenal disease.[4,13,14] Also, the incidence of late postoperative problems is similar to that observed following truncal vagotomy with antrectomy. It is, however, indicated for a potentially difficult duodenal stump or in the surgical management of a bleeding or perforated prepyloric ulcer in an unstable patient, after adequate biopsy samples have been obtained. The addition of ulcer excision did not improve the recurrence rate in our series, as one of the nine patients so treated had recurrent ulcer.

Highly selective vagotomy has gained a place in the management of uncomplicated duodenal ulcer,[15,16] but recurrence rates following this procedure for gastric ulcer are unacceptable.[2,3,15,16] Although Reid and colleagues,[17] in a randomized clinical trial, found no difference in recurrence rates between Billroth I resection and resection of the ulcer with highly selective vagotomy, the recurrence rate in the gastrectomy group was unusually high compared with those of most other series. Prepyloric and pyloric canal ulcers appear to be especially resistant to resolution by highly selective vagotomy.[2,3] Our series corroborates these data, with a 33% recurrence rate following the use of highly selective vagotomy for gastric ulcer.

Although wedge resection of the ulcer provides enough tissue to exclude malignant disease, the recurrence rate in our series was far greater than that following gastric resection, with the same potential for postoperative suture-line leakage and infection. Damage to the adjacent nerves of Latarjet is not unexpected and could account for the two cases of delayed gastric emptying following wedge resection in our series.

Acutely perforated gastric or duodenal ulcers present a similar clinical picture, but in addition to the potential for malignancy in gastric ulcer, the often-advanced age of the patient, with associated medical disease, may contraindicate aggressive surgical management. Always a consideration in the management of visceral perforation is the degree of intraperitoneal contamination with the potential for intra-abdominal sepsis and suture-line breakdown. Of interest in our series was the high incidence of negative cultures from intraperitoneal fluid, even in patients with a history indicative of perforation 12 hours or more before surgery. A similar incidence of negative cultures has been noted by Boey and colleagues,[18] suggesting that extensive or long-standing peritoneal contamination does not contraindicate a definitive procedure for perforated peptic ulcer.

Because of the high recurrence rate after omental patching, gastric resection is clearly the operation of choice for gastric perforation. However, when resection is contraindicated as in the unstable elderly patient with underlying medical illness, patching may be the only alternative.[19] Intraoperative biopsy and then long-term therapy with histamine$_2$ blockers are suggested before more definitive surgery is considered in the event of recurrence.

A substantial number of perforated gastric ulcers are located in the antrum and prepyloric area where they share the physiologic characteristics of duodenal ulcer. In these circumstances the addition of a truncal vagotomy is appropriate, despite the risk of complications postoperatively.

When surgery is required for bleeding gastric ulcer, our series suggests that anything less than resection of the ulcer, as a gastrectomy, results in a high incidence of recurrent bleeding in the early postoperative period. This must be kept in mind when choosing a lesser procedure in high risk, unstable or elderly patients in whom the operative death rate of a second procedure can be extremely high. As in duodenal ulcer, optimal management of bleeding gastric ulcer depends on prompt recognition and the timing of surgery.

Conclusions

When considering operative treatment for gastric ulcer in either elective or emergency situations, the surgeon must recognize the possibility of malignant disease and rule it out by tissue sampling endoscopically or at laparotomy. Gastric resection is the procedure of choice in both emergency and elective situations, with the addition of truncal vagotomy, when indicated by location of the ulcer or the results of preoperative acid secretory studies. In the emergency setting, when the patient is unstable or a poor risk, a less-definitive procedure may be undertaken providing the increased incidence of ulcer recurrence is anticipated.

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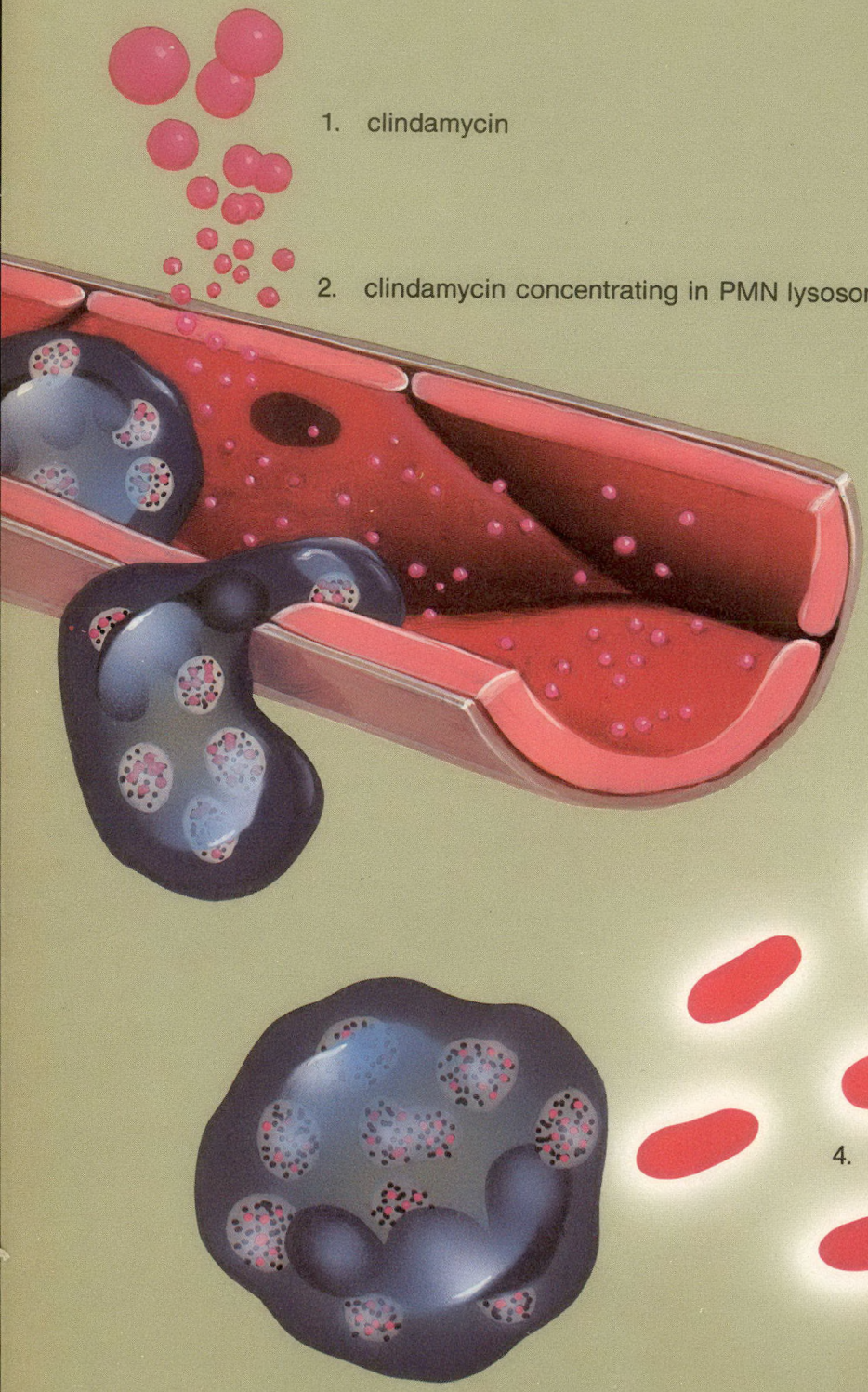

1. clindamycin
2. clindamycin concentrating in PMN lysosomes
3. clindamycin-laden PMN moving toward the site of infection
4. the invading bacteria

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enhances HOST DEFENSE

Recent *in-vitro* research has shown that clindamycin concentrates within the PMN in amounts greater than are found outside of the PMN.[1] The rates of chemotaxis, phagocytosis and killing of bacteria by PMNs are also enhanced by the presence of this antibiotic.[2,3] These characteristics may help explain clindamycin's outstanding record of clinical efficacy in both anaerobic and gram-positive aerobic infections.

Since host defense factors may be crucial in determining the outcome of an infection, selection of antibiotics based on host defense parameters may become a trend in infectious disease therapy.

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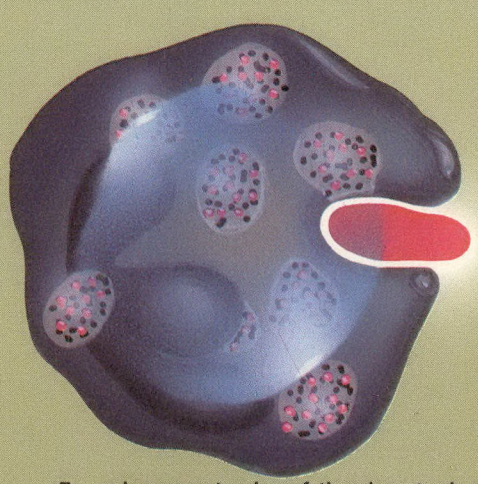

5. phagocytosis of the bacterium by antibiotic-enhanced PMN

6. degranulation and killing of engulfed bacterium

For prescribing information see page 238

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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 microaerophilic 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.

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.

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 occurring 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.

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.

Is 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 indicated by the clinical situation.

As with all antibiotics, perform culture and sensitivity studies in conjunction with drug therapy.

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 abscesses.

(b) *Intravenous Infusions:* Of 192 patients treated 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 conjunction 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 and 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 occurred 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 dilution of 300 mg in 50 ml of diluent (6 mg/ml) or more, 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	100 ml	20 min.
900 mg	150 ml	30 min.
1200 mg	200 ml	45 min.

Alternatively, 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. In severe infections, it is recommended that children be given no less than 300 mg/day regardless of body weight. (Dilute Dalacin C Phosphate Sterile Solution in the same manner as for adults.)

Dilution and Compatibility:

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 (Hartmann's Solution)

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.

Supplied:

Dalacin C Phosphate contains the following per ml of sterile solution:

- 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.

Dalacin C Phosphate is available in 2 ml and 4 ml ampoules.

NOTE: Do not store below 15°C.

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DENIS BERNARD, MD, FRCSC; STEPHEN MORGAN, MD, FRCSC; DANIEL TASSÉ, MD, FRCSC

Colonoscopic Assessment of Radiologic Strictures of the Colon

The authors studied 47 patients with radiologic evidence of stricture to determine whether colonoscopy in this situation increased the accuracy of diagnosis and how this procedure might influence patient management. Colonoscopy increased to 81% the diagnostic accuracy, which was established at 38% with the single-contrast enema. Failure of both techniques to establish a precise diagnosis was 19%.

From the clinical and radiologic data, surgical exploration for the 47 strictures would have been necessary in 28, not indicated in 9, and indicated solely for diagnostic purposes in 10. The addition of colonoscopy prevented unnecessary laparotomy in 5 (18%) of the first group and in 8 (80%) of the last. The authors conclude that colonoscopy should be complementary to the standard radiologic examination for colonic strictures, especially when carcinoma is suspected or if roentgenography does not provide a definitive diagnosis.

L'évaluation par coloscopie de 47 sténoses radiologiques du côlon a été faite pour établir une corrélation entre les diagnostics radiologiques, endoscopiques et finaux et pour déterminer si la conduite thérapeutique a pu être influencée par l'addition de la coloscopie. Le diagnostic radiologique a été exact et précis dans 18 cas (38%). L'addition de la coloscopie a permi d'accroître ce taux d'exactitude à 81% (20 cas additionnels).

L'indication chirurgicale qui avait été posée 28 fois sur des critères cliniques et radiologiques a été infirmée par la coloscopie chez cinq et différée chez neuf autres. De plus, une intervention chirurgicale a pu être évitée à raison huit fois mais à tort une fois chez 10 patients ou l'indication chirurgicale ne reposait que sur un doute diagnostique radiologique.

À cause d'un taux résiduel de 19% de diagnostic inexact ou imprécis, on doit considérer la coloscopie comme complémentaire à la radiologie dans les sténoses et l'élément clinique ne doit pas être ignoré.

Strictures of the large bowel seen radiologically may or may not represent a serious pathologic condition. Spasm, muscular thickening, fibrosis, inflammation and carcinoma can all be manifested by narrowing of the colonic lumen. Although there may be typical radiologic features for each lesion, in many cases a diagnostic dilemma persists,[1,2] especially when carcinoma cannot be ruled out. Before the advent of colonoscopy, the only approaches to these strictures were to observe the patient by repeated barium enema roentgenography or to operate, both of which had obvious disadvantages. Even with the more widespread use of air-contrast enemas, the tortuous sigmoid colon, the commonest site of strictures,[1] is not easily completely demonstrated.[3]

The purpose of this paper is to determine the extent to which colonoscopy can add to the diagnostic accuracy and influence subsequent surgical management of the patient.

Patients and Methods

Between 1980 and 1984, we attempted colonoscopy in every patient under our care who had radiologic evidence of colonic stricture. We excluded those with the typical symptomatic annular, "apple-core" lesion, because there is no doubt as to the diagnosis of carcinoma, and the typical filiform narrowing in patients who had recurrent Crohn's disease. There were 47 patients (20 men, 27 women) whose mean age was 59 years.

Single-contrast radiologic examinations were performed initially with barium, or water-soluble material in acute cases. The opinions were those of the radiologist's written report. Colonoscopy was subsequently performed with an Olympus CF-LB3R instrument (Olympus Corp. of America, New Hyde Park, NY) with x-ray films on display during the procedure. Fluoroscopy was not used. The diagnosis was established in all but one patient, either by surgical exploration and pathological examination of the resected bowel, endoscopic biopsy or, in non-operated cases, through a combination of history, endoscopic findings and follow-up (e.g., asymptomatic normal bowel).

Before colonoscopy an indication for surgery was made from the clinical features (persistent or disabling symptoms, presence of a mass, signs of bowel obstruction) or the radiologic diagnosis or a suspicion of carcinoma; the indication in each case was considered to be either present, absent or doubtful (when no diagnosis could be made). After colonoscopy we reassessed our findings to determine if surgery was indeed necessary, not necessary, necessary but could be delayed, or whether the colonoscopic findings were inconclusive.

Findings

As expected the sigmoid colon was the most common site of stricture in 33 (70%) patients (Table I). A summary of all cases, with radiologic diagnoses, colonoscopic findings, final diagnosis and indi-

Table I—Site of Stricture in 47 Patients

Site	No. of patients (%)
Sigmoid colon	33 (70.2)
Descending colon	7 (14.9)
Splenic flexure	2 (4.3)
Transverse colon	1 (2.1)
Ascending colon	1 (2.1)
Cecum	1 (2.1)
Ileocolonic anastomosis	2 (4.3)

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cation for surgery before and after colonoscopy are shown in Table II. A definitive diagnosis of diverticulitis was made radiologically in 11, and of carcinoma in 9, but in most other cases the radiologic findings were equivocal and offered a wide variety of diagnoses. Figures 1 to 6 illustrate the varying radiologic findings in these patients. The distribution of final diagnoses established by laparotomy, endoscopic biopsy or a combination of history, endoscopy and follow-up are shown in Table III.

The radiologic diagnosis correlated with the final diagnosis in 18 cases (38%). The endoscopist was right in 14 of these cases, uncertain in 2 (cases 12 and 41) and could not reach the stricture in 2 cases of carcinoma (cases 15 and 16). The radiologist's opinion did not correlate in 13 cases. The colonoscopist made the correct diagnosis in nine of these, erred in two (cases 24 and 39), one of which was a patient with carcinoma, remained doubtful in one (case 40) and could not reach the stenosis in one (case 17, normal bowel on barium follow-through). Finally, barium enema examination was not diagnostic in 16 (34%) (cases 25 to 34 and 42 to 47). Of these, colonoscopy resulted in the

Table II—Summary of Diagnostic Investigations in 47 Cases of Colonic Stricture

Case no.	Sex	Age, yr	Site of stenosis	Radiologic diagnosis	Colonoscopic impression	Final diagnosis	Surgical indication	
							Before colonoscopy†	After colonoscopy‡
1	M	63	Sigmoid	DIV	DIV	DIV	–	–
2	F	61	Sigmoid	DIV	DIV	DIV	–	–
3	M	68	Sigmoid	DIV	DIV	DIV	–	–
4	F	76	Sigmoid	DIV	DIV	DIV	–	–
5	F	42	Sigmoid	DIV	DIV	DIV	+	+D
6	F	57	Sigmoid	DIV	DIV	DIV	+	+D
7	F	70	Sigmoid	DIV	DIV	DIV	+	+D
8	M	69	Sigmoid	DIV	DIV	DIV	+	+D
9	F	63	Sigmoid	DIV	DIV	DIV	+	+D
10	F	61	Sigmoid	DIV	Anastomotic stenosis	Anastomotic stenosis	–	–
11	F	56	Sigmoid	DIV	N	N	?	0
12	F	73	Sigmoid	CA	? not diagnostic	CA	+	+
13	M	63	Sigmoid	CA	CA	CA	+	+
14	F	67	Sigmoid	CA	CA	CA	+	+
15	M	75	Transverse colon	CA	Not reached	CA	+	+
16	M	63	Descending colon	CA	Not reached	CA	+	+
17	F	78	Ileotransverse anastomosis	CA	Not reached	N	+	0§
18	F	67	Splenic flexure	CA	N	N	+	0
19	F	47	Descending colon	CA	N	N	+	0
20	M	77	Sigmoid	CA	DIV	DIV	+	0
21	F	63	Sigmoid	DIV and CA	DIV and CA	DIV and CA	+	+
22	M	61	Descending colon	Lymphoma	DIV	DIV	+	+
23	F	61	Sigmoid	DIV and polyp	DIV	DIV	–	–
24	M	70	Sigmoid	DIV and polyp	DIV and polyp	DIV	+	+
25	M	48	Sigmoid	DIV or CA	DIV	DIV	+	+D
26	F	78	Sigmoid	DIV or CA	DIV	DIV	+	+D
27	F	67	Sigmoid	DIV or CA	DIV	CA	+	+
28	M	62	Sigmoid	DIV or CA	DIV	Foreign-body perforation	+	+
29	M	60	Sigmoid	DIV or CA	N	N	?	0
30	M	29	Descending colon	Inflammation or CA	Crohn's disease	Crohn's disease	+	+
31	M	55	Descending colon	Inflammation or CA	Ischemic colitis	Ischemic colitis	+	0
32	F	47	Sigmoid	Crohn's disease or CA	Crohn's disease	Crohn's disease	?	0
33	M	37	Descending colon	Inflammation or ischemia	Inflammation	Pancreatitis	?	?
34	F	65	Sigmoid	Inflammation or fibrosis	Radiation stenosis	Radiation stenosis	–	–
35	M	37	Ileotransverse anastomosis	Anastomotic stenosis	Crohn's disease	Crohn's disease	+	+D
36	F	71	Sigmoid	Postop changes	Anastomotic band	Anastomotic band	–	–
37	F	61	Descending colon	Ulcerative colitis	Ulcerative colitis	Ulcerative colitis	+	+
38	F	44	Sigmoid	Spasm	Fibrosis	Fibrosis after seat-belt injury	?	0
39	F	72	Sigmoid	Extracolonic origin	Extracolonic	CA	?	0
40	F	39	Sigmoid	Extracolonic origin	Extracolonic	Endometriosis	+	+D
41	M	19	Ascending colon	Extracolonic origin	Extracolonic	Unknown*	?	0
42	M	56	Sigmoid	? not diagnostic	CA	Extracolonic (carcinomatosis)	+	+
43	F	38	Sigmoid	? not diagnostic	DIV	Endometriosis	+	+
44	F	48	Cecum	? not diagnostic	Crohn's disease	Crohn's disease	–	–
45	M	75	Sigmoid	? not diagnostic	Anastomotic stenosis	Anastomotic stenosis	?	0
46	F	58	Splenic flexure	? not diagnostic	N	N	?	0
47	M	62	Sigmoid	? not diagnostic	N	N	?	0

DIV = diverticulitis, CA = carcinoma, A = anastomosis, N = normal bowel.
*Congenital bands suspected because of age, location, no intraluminal disease, no symptoms; surgery not indicated.
†+ = present, – = absent, ? = doubtful, indicated for diagnostic purpose only.
‡+ = still present, – = still absent, 0 = no longer present, +D = still present but delayed.
§Final diagnosis established by barium follow-through examination.

correct diagnosis in 11, but was incorrect in 4 (cases 27, 28, 42 and 43) and was equivocal in 1 (case 33).

Barium enema examination alone resulted in the correct diagnosis in 18 out of 47 patients. When the 20 correct diagnoses obtained at colonoscopy in the remaining 29 are added, the combined accuracy of both techniques totals (81%) (38 of 47).

As to management of the patients, the indication for surgery was present before colonoscopy in 28 patients, absent in 9 and doubtful or indicated for diagnosis only in 10. In the 28 patients for whom surgery was initially indicated, that indication was still present after colonoscopy in 14, it was still present, but could be delayed to a more appropriate time in 9, and was no longer present in 5 (normal bowel 3, cases 17, 18, 19; diverticulitis, case 20; ischemic colitis, case 31). In the nine patients presenting no indication for surgery before colonoscopy, none was established later. Finally in the other 10 patients in whom the indication for surgery was doubtful, it was considered not indicated in 8, indicated in 1 (case 42) and remained doubtful in 1 (case 33) following colonoscopy. Further investigation of the last patient led to a diagnosis of chronic pancreatitis and surgical exploration was carried out.

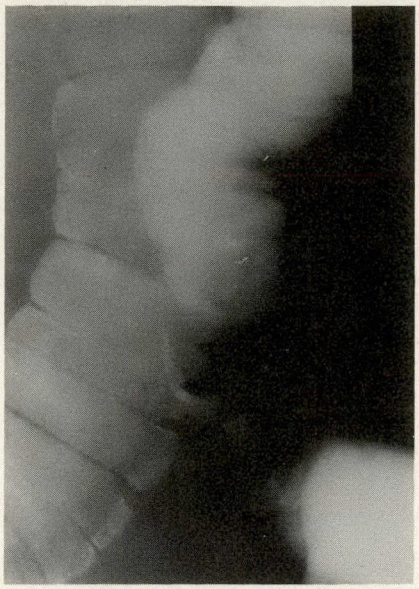

FIG. 1—Case 31. Radiologic appearance suggests inflammatory condition but carcinoma could not be ruled out. Endoscopic and histologic features were consistent with ischemic colitis and stricture.

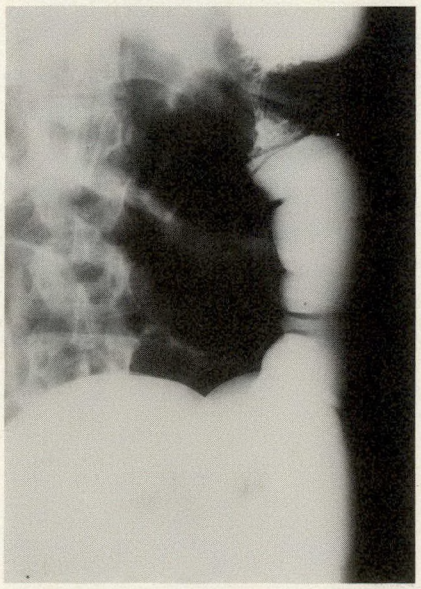

FIG. 2—Case 33. Inflammation or ischemia was suggested radiologic diagnosis. Endoscopic findings were of inflammation of unknown cause. Subsequent exploration revealed pancreatitis and extrinsic compression.

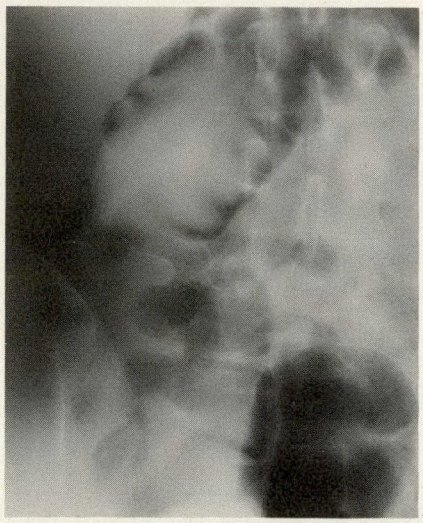

FIG. 3—Case 41. Radiologic and endoscopic diagnosis was extracolonic disease. There was no known final diagnosis, but congenital bands were suspected because of patient's young age (19 years), location of stricture and because there were no symptoms and no intraluminal disease. Patient was not operated on.

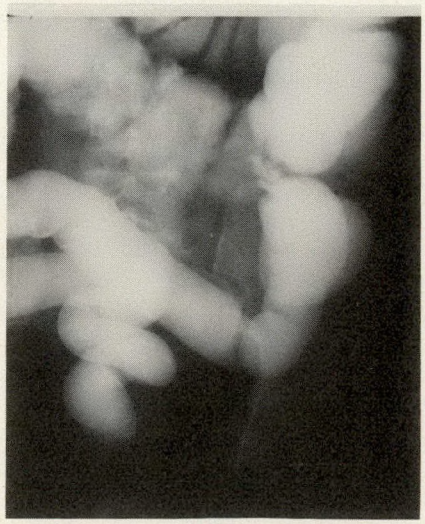

FIG. 4—Case 19. Findings are suggestive of carcinoma but bowel appeared normal at endoscopy.

Discussion

Most important in the diagnosis and treatment of stenotic lesions of the large bowel is to establish the presence or absence of a malignant condition. Both diverticular disease and carcinoma occur most commonly in the sigmoid colon where they may coexist and be very difficult to differentiate. In our study, roentgenography established a diagnosis of diverticulitis in 12 cases, later confirmed in 10. Colonoscopy suggested the correct diagnosis in all 12 but was definitive in only 2, neither being a carcinoma. This is contrary to the experience of Boulos and associates[4] who reported coexistent neoplasia, benign or malignant, in 31% of radiologically demonstrated diverticular disease. Carcinoma

FIG. 5—Case 27. Roentgenography could not differentiate diverticulitis from carcinoma and endoscopic examination suggested a diagnosis of diverticulitis. Final diagnosis was carcinoma.

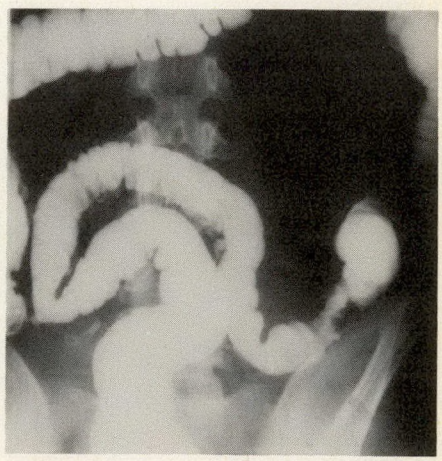

FIG. 6—Case 25. Radiologic appearance suggested either diverticulitis or carcinoma. Endoscopy ruled out carcinoma.

(or lymphoma) was thought to be present on 11 contrast enema examinations: 5 were subsequently proven incorrect, 4 by colonoscopy (cases 18, 19, 20 and 22). The suspicious area in the fifth could not be reached by colonoscopy. These findings are comparable to the experience of Hunt and colleagues[1] who disproved the presence of carcinoma in 30 (57%) of 53 "malignant strictures". Filoche and colleagues[5] also reported colonoscopic exclusion of carcinoma in 7 of 13 (54%) suspected cases. Diverticulitis could not be differentiated from carcinoma in five instances: carcinoma was present in one but was missed at colonoscopy (case 27, Fig. 5); in the other four, suspected carcinoma was not present (Fig. 6). This follows the experience of Rozen's group;[6] in 18 similar situations Filoche and colleagues[5] found only one case of carcinoma.

A limitation of colonoscopy in strictures is well demonstrated in the study of Dean and Newell[3] in which there were 17 (47%) inadequate examinations of the diseased segment in 36 cases of diverticulitis. Their main reasons for failure were sharp angulation, inability to distend the narrow lumen and persistent fecal soiling through the obstructed segment. Filoche and colleagues[5] established at 20% the number of strictures that could not be examined over their whole length. In our study, an accurate diagnosis by endoscopy failed in three situations: when the segment was too narrow to permit thorough examination (cases 12, 27 and 39), when it was impossible to reach the level of the stricture (cases 15, 16 and 17) and when extraluminal disease was present (cases 28, 33 and 40 to 43).

We were particularly concerned about seven (15%) patients with normal bowel who underwent colonoscopy because some form of narrowing had been seen on roentgenograms; in four carcinoma had either been diagnosed or suspected (Fig. 4). Colonoscopy showed normal bowel in six, and in the other (case 17) we relied on the result of barium follow-through examination. Hunt and associates[1] had a similar experience. Another important asset of colonoscopy in strictures is the clarification of nondescript radiologic pictures. Among 16 (34%) such cases, colonoscopy was decisive in 11; extracolonic disease was present in 4. In the remaining case (no. 27 in Table II) carcinoma was present but not seen at endoscopy.

Table III—Final Diagnosis in 47 Cases of Colonic Stricture

Diagnosis	No. of patients (%)
Diverticulitis (Fig. 6)	15 (32)
Carcinoma (Fig. 5)	7 (15)
Diverticulitis and carcinoma	1 (2)
Anastomotic stenosis	2 (4)
Endometriosis	2 (4)
Crohn's disease	4 (9)
Ulcerative colitis	1 (2)
Ischemic colitis (Fig. 1)	1 (2)
Radiation stenosis	1 (2)
Anastomotic band or bridge	1 (2)
Ingested foreign-body perforation	1 (2)
Fibrosis after seat-belt injury	1 (2)
Extrinsic	3 (6)
Pancreatitis (Fig. 2)	1
Carcinomatosis	1
? (congenital bands) (Fig. 3)	1
Normal bowel (Fig. 4)	7 (15)

Neither roentgenography nor endoscopy could establish the correct diagnosis in nine cases (19%). Every clinician knows that the interpretation of radiologic and endoscopic findings must take into account the clinical picture. A decision on the management of a patient with stricture must follow these principles.

Colonoscopy influenced the surgical decision in two clinical settings. First, it allowed surgery to be deferred to a more appropriate time. In most of these cases the patients had diverticulitis or other inflammatory conditions in the acute phase. The delay allowed for a more favourable surgical condition. Second, colonoscopy removed the need for surgical exploration that would have been undertaken either because carcinoma was suspected or for diagnostic purposes only. Both Hunt and associates[1] and Rozen and colleagues[6] have stated the usefulness of colonoscopy in avoiding unnecessary laparotomies.

To our knowledge colonoscopy wrongly influenced the surgical decision in only one patient (case 27, Fig. 5) in whom carcinoma was suspected but mistakenly ruled out. Surgery was eventually performed but after a 2-month delay. Filoche and associates[5] mentioned a similar case, illustrating the need to consider radiology and endoscopy as complementary procedures in the investigation of a patient clinically suspected of having large bowel disease.

Summary and Conclusions

Narrowing of the colonic lumen may result from a wide range of diseases. In our study of 47 patients, radiologic demonstration of colonic stricture by single-contrast examination gave the correct diagnosis in 38%. Colonoscopy increased the accuracy of diagnosis to 81%. Both radiologic and colonoscopic examinations failed to achieve the right diagnosis in 19%.

The decision to operate based on clinical or radiologic criteria may lead to unnecessary laparotomies or untimely surgery. Colonoscopy did not confirm the indication for operation in 18% of such cases and afforded a useful delay in 32%. Colonoscopy also avoided an unnecessary laparotomy in 80% of patients in whom surgical exploration was being considered for diagnostic purposes.

Colonoscopy should complement a contrast enema in every case of colonic stricture.

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Palliative Percutaneous Transhepatic Biliary Drainage: Assessment of Morbidity and Mortality

The results of palliative percutaneous transhepatic biliary drainage were assessed retrospectively in 16 cases and prospectively in 7 between 1982 and 1985. Causes of biliary obstruction were metastatic cancer (nine), pancreatic cancer (nine), cholangiocarcinoma (three) and gallbladder cancer (two). Internal drainage was established in 78.3%. In the 19 patients who died, the mean duration of drainage was 3.6 months. Early morbidity was 17.4%. Late septic morbidity occurred in 11 patients (48%) (a total of 28 episodes). Late deaths (31.2%) resulted from upper gastrointestinal hemorrhage, hepatic abscess, septic shock, subhepatic abscess and peritonitis.

Percutaneous transhepatic biliary drainage is associated with substantial morbidity (67.4%) and mortality (35.5%) from infection. Palliation was modest; only eight patients spent more than half their survival time at home, and 10 patients never left hospital. Clinical trials are required to assess the risk-to-benefit ratio and role of percutaneous transhepatic biliary drainage versus surgical bypass in patients with lesions amenable to surgery, and biliary drainage versus no treatment in patients whose tumour cannot be bypassed.

Les résultats palliatifs du drainage biliaire transhépatique percutané ont été évalués rétrospectivement dans 16 cas et prospectivement dans 7 autres cas traités entre 1982 et 1985. Parmi les causes d'obstruction biliaire, on note les métastases (neuf cas), le cancer du pancréas (neuf), le cholangiocarcinome (trois) et le cancer de la vésicule biliaire (deux). Un drainage interne a été établi dans 78.3% des cas. Chez les 19 patients qui sont décédés, la durée moyenne de drainage a été de 3.6 mois. Une morbidité précoce a été vue dans 17.4% des cas. Des incidents septiques retardés sont survenus chez 11 patients (48%) (un total de 28 épisodes). Les décès tardifs (31.2%) ont été causés par une hémorragie gastrointestinale supérieure, un abcès hépatique, un choc septique, un abcès sous-hépatique et une péritonite.

Le drainage biliaire transhépatique percutané est entaché d'une morbidité (67.4%) et d'une mortalité (35.5%) importantes résultant de l'infection. L'effet palliatif fut modeste; seulement huit patients ont passé plus de la moitié de leur temps de survie à domicile, et 10 autres n'ont jamais quitté l'hôpital. Des essais cliniques sont jugés nécessaires pour établir le rapport risques/bénéfices et préciser le rôle du drainage biliaire transhépatique percutané par rapport à la dérivation chirurgicale chez les patients opérables; de même, il faudrait évaluer les mérites respectifs du drainage biliaire et de l'absence de traitement chez les patients dont la tumeur ne permet pas une opération de pontage.

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The use of percutaneous transhepatic biliary drainage to treat malignant obstruction of the bile ducts has gained popularity in the last decade. Since Molnar and Stockum[1] reported the first successful case of internal drainage in 1974, radiologists have developed and refined techniques to decompress the biliary tree.[2–6]

McPherson and colleagues[7] and Ellison and associates[8] have cautioned that while this procedure has gained rapid acceptance, the risk-to-benefit ratio must be carefully assessed. Further, its morbidity and mortality have yet to be compared with those of other modes of treatment for malignant obstruction of the biliary tree, in a prospectively randomized controlled clinical trial.

The present report considers the morbidity and mortality associated with percutaneous transhepatic biliary drainage in 23 cases of malignant obstruction of the biliary tree. We paid particular attention to the palliative benefit of the procedure and to the morbidity from infectious and other complications.

Patients and Methods

We reviewed the charts of 16 patients who had undergone percutaneous transhepatic biliary drainage between August 1982 and June 1984. We also studied prospectively seven patients who had undergone the same procedure between July 1984 and January 1985. In all there were 15 men and 8 women with a mean age of 68.6 years (range from 31 to 94 years). All had malignant obstruction of the biliary tract (Table I).

The data collected concerned previous surgery, the cause and location of obstruction, the date, duration and type of drainage, the occurrence of all complications and the date and circumstances of death. To identify biliary microbiology and the pathogens involved in infection, we took serial bile samples for aerobic and anaerobic culture on the day of biliary drainage and then at the time of monthly catheter changes or when otherwise clinically indicated in the prospective group. Whenever possible, we recorded microbiologic findings on the retrospective cases.

Finally, the benefit of percutaneous transhepatic biliary drainage was assessed with respect to the amount of time spent at home between the day of drainage and death and the number of hospitalizations required during this time.

Drainage Technique

We used a modification of the techni-

Table I—Causes of Obstructive Jaundice

Cause	No. of patients*	
Metastatic cancer		9 (4)
Colon	4 (2)	
Stomach	3 (2)	
Breast	1	
Prostate	1	
Pancreatic cancer		9 (6)
Cholangiocarcinoma		3 (3)
Gallbladder cancer		2 (2)
Total		23 (16)

*Numbers in brackets represent patients with tissue diagnosis of the cause of obstructive jaundice.

que previously described by Ferrucci and colleagues,[5] Nakayama and associates,[6] and Ring's group.[9] Standard fine-needle cholangiography was first performed to identify the location and assess the extent of obstruction. The modified Cope catheter system (20 gauge) was used to gain access to the biliary tree. If there was no cholangitis, internal drainage was attempted. If that was unsuccessful a straight catheter was left in the most dependent segment of the biliary tree and another attempt made in 2 to 4 days, with external drainage in the interim. Whether or not the catheter had been placed beyond the obstruction, external drainage was maintained for the first 24 hours, followed by progressive clamping, resulting, in successful cases, in complete internal drainage within 8 days. During this time, catheters were flushed four times daily with 10 ml of normal saline, the frequency was reduced to once daily when internal drainage was established. Catheters were changed each month on an outpatient basis unless otherwise indicated. Antibiotics were not given prophylactically unless patients had had a previous episode of catheter-related cholangitis, known bactibilia, or previous biliary tract surgery.

Findings

In 9 of the 23 patients percutaneous transhepatic biliary drainage was undertaken because a surgical bypass could not be done. Laparotomy to assess the possibility of surgical bypass was not performed in 14 patients, 7 of whom had metastatic biliary tract obstruction. Of the remaining seven, two were pre-terminal (both died within 6 weeks of presentation), two were shown radiologically to have lesions that could not be bypassed (obstruction at the porta hepatis), one refused surgery and two underwent biliary drainage because of the surgeon's preference, despite radiologic evidence that surgical bypass might be possible. Two of these 14 patients subsequently had operative bypass when biliary drainage failed, and their courses are described below.

There were no failures of insertion of the transhepatic catheters in 23 attempts. Internal drainage was established initially in 15 patients and within 4 days in 3 others for an overall success rate of 78.3% (18 of 23). Five patients (21.7%) had external drainage only.

The average duration of drainage was 3.6 months (range from 4 days to 14 months) among the 19 patients who died. Two of the four patients alive at the time of reporting have been drained for 1 and 4 months respectively. A third patient has undergone surgical bypass, despite metastatic gastric cancer, for repeated attacks of cholangitis. The fourth patient, initially drained percutaneously because of surgeon's preference, underwent surgical bypass because of persistent fever and intrahepatic abscesses.

Complications

Early complications of percutaneous transhepatic biliary drainage included catheter dislodgement, cholangitis and fatal acute hemorrhagic pancreatitis (Table II). None of these complications required operative intervention. The early morbidity was 17.4% (4 of 23) and the rate of early death 4.3% (1 of 23).

Thirty late complications occurred in 22 patients (1.4 complications per patient). Late morbidity from catheter blockage and dislodgement occurred in 34.9% and 13.0% of patients respectively. Cholangitis occurred late 19 times in 11 patients (1.7 episodes per patient) and was associated with bacteremia five times, resulting in the death of one patient. Three episodes of cholangitis occurred within the first 3 weeks of drainage in the patient with metastatic stomach cancer mentioned above; operative choledochoenterostomy resolved the infections. Eight months later, the intrahepatic bile ducts became obstructed from progression of disease, and two catheters were required to treat recurrent cholangitis due to the original organism (*Klebsiella*).

Five patients had septic-related deaths. At autopsy two were found to have intrahepatic abscesses and a third had a subhepatic abscess. Autopsy was not performed on the other two, but in both the catheters were known to be providing inadequate drainage of the left-sided bile ducts in one case and of both left and right-sided ducts in the other.

The late death rate related to percutaneous transhepatic biliary drainage was 31.2% (7 of 22) (Table II). An eighth patient died of acute myocardial infarction while recovering from an episode of cholangitis.

Bile cultures in 16 patients at the time of initial drainage were negative in 11 (68.8%) patients and positive in 5 (31.3%) (Table III). Cultures were not obtained in the other seven patients. Three of the

Table II—Complications of Percutaneous Transhepatic Biliary Drainage

Complication	Early, no. of episodes/ no. of patients	Late, no. of episodes/ no.of patients	Deaths*
Minor			
Catheter blockage	0	12/8	–
Catheter dislodgement	1/1	3/3	–
Major			
Cholangitis	2/2	19/11	–
Bacteremia	–	5/5	1
Hepatic abscess	–	2/2	2
Subhepatic abscess	–	1/1	1
Purulent ascites	–	1/1	1
Acute pancreatitis	1/1	–	1
Upper gastrointestinal tract hemorrhage	–	2/2	2

*One other patient recovering from an episode of cholangitis died of acute myocardial infarction.

Table III—Microorganisms Found in Bile*

Organism	Day of drainage	Post drainage
Klebsiella sp	2 (2)	10 (7)
Enterobacter	1	10 (6)
Escherichia coli	2	7 (5)
Enterococcus	3 (2)	7 (6)
Proteus mirabilis	0	6 (5)
Pseudomonas aeruginosa	0	6 (2)
Streptococcus sp, Lancefield group D, non-enteric	1	4 (1)
Staphylococcus epidermidis	0	4 (0)
Clostridium perfringens	1 (1)	3 (2)
Corynebacterium sp	0	3 (0)
Acinetobacter sp	0	2 (0)
Citrobacter sp	0	1 (2)
Microaerophilic streptococci	0	1 (1)
Aeromonas hydrophila	0	1 (0)
Hafnia sp	0	2 (2)
Staphylococcus aureus	1	1 (1)
Streptococcus sp, Lancefield group B	0	1 (1)

*Numbers in brackets indicate the number of times a microorganism was implicated in an episode of cholangitis.

five positive cultures were in patients who had undergone previous biliary tract surgery.

Bile cultures remained negative in 3 of the 11 patients, but became positive in 6, representing a conversion rate of 54.5%. In the remaining two cases, follow-up cultures were not obtained. The biliary trees that remained sterile were in patients who died within 3 weeks of drainage.

The palliative effects of percutaneous transhepatic biliary drainage with respect to improvement in hyperbilirubinemia, pruritis and anorexia are shown in Table IV and the duration of time spent at home in Table V.

Discussion

All patients who underwent percutaneous transhepatic biliary drainage in this series had malignant obstruction of the biliary tract. Internal drainage was established in 18 (78.3%) of 23 patients which compares favourably with the rates of 72% and 64.3% reported by Mueller and associates[2] and Clark and colleagues[10] respectively. The average duration of drainage was 3.6 months compared with 4.3 months and 3.3 months reported by Ferrucci and colleagues[5] and Pollock's group[4] respectively. Early morbidity (17.4%) and mortality (4.3%) also compared favourably with those of other studies.[10,11]

The single early death due to pancreatitis represents the only one reported to date from this complication, although at least three other cases of pancreatitis related to percutaneous transhepatic biliary drainage have been reported.[3,12] Early death from bleeding (five patients), pneumothorax with bilious pleural effusion (one) and septic shock (one) have also been reported.[2,3,10,13] Intra-abdominal hemorrhage, hemobilia, bilothorax or bile leak, reported by others did not occur in our series. This might be accounted for in part by the use of a smaller (20 gauge) needle for cannulation.

Late morbidity from cholangitis occurred in 50% of patients, somewhat higher than previously reported (range of 14.5% to 36.5%[2–4,6,7,11,13]). The 30-day mortality, related to biliary drainage was 35.0% (8 of 23) and compares with rates quoted for surgical bypass, which range from 6% to 30%.[14,15]

The prophylactic use of antibiotics has been advocated by several investigators,[3,9–11] none of whom have been able to demonstrate a decreased incidence of morbidity from infection. Nevertheless, antibiotics should be given prophylactically to patients with a history of biliary tract surgery or instrumentation, with a periprocedural history suggestive of cholangitis, and to those who undergo catheter change or manipulation. As Keighley and colleagues[16,17] and Wayne and Whelan[18] have pointed out, morbidity from contaminated bile can be important; thus Wayne and Whelan recommended prophylaxis with a combination of an aminoglycoside and ampicillin.

Our practice has been to use a first-generation cephalosporin for initial prophylaxis and for subsequent manipulations in patients who have experienced no morbidity from infection. The appropriate antibiotic(s) in those who have suffered infectious morbidity should be directed by the most recent bile or blood culture. Based upon the paucity of anaerobes cultured in either bile or blood of our patients, anaerobic coverage was not warranted and is not recommended.

The average duration of drainage of 3.6 months is misleading, since patients fell into three distinct groups with respect to survival (Table V). Eight patients lived less than 1 month after biliary drainage and only one was discharged from hospital before death. Five patients lived from 1 to 4 months. While two were home for at least 51% of their remaining days, the other three never left hospital. Of the eight patients who lived for 4 or more months, 6 spent a minimum of 51% of their remaining days at home, whereas the other one spent only 6.6% of such time at home. These eight patients required an average of 1.4 hospitalizations after their drainage procedures, to treat cholangitis. The palliative benefit of drainage is most evident in this group of patients. While they had serious morbidity (eight episodes of tube blockage, nine episodes of cholangitis, three episodes of bacteremia and two hepatic abscesses), four spent more than 75% of their remaining days out of hospital and two others between 51% and 75%.

The morbidity from infection after percutaneous transhepatic biliary drainage is high enough in this and other series[7,11,13] to cast doubt on its overall palliative benefit in all but a select group of patients likely to survive for several months.

Of patients presenting with carcinoma of the pancreas or periampullary region, less than 20% have surgically resectable lesions.[14,15] Operative bypass is possible in another 30%. Thus approximately 50% of patients are left with a palliative drainage procedure or no treatment for their disease. For patients who have biliary obstruction due to metastatic disease, curative resection is inappropriate, and in less than 30% will surgical bypass be possible because of the higher incidence of associated portal lymph-node involvement. Therefore, more than 50% of these patients may be candidates for a palliative drainage procedure of some sort.

The ideal trial would randomize patients with surgically bypassable lesions to surgery or a nonoperative drainage procedure. For those in whom surgical bypass cannot be performed safely, randomization between a nonoperative drainage procedure and no treatment should be undertaken. Since morbidity and mortality from infection using percutaneous transhepatic biliary drainage is high, it would be prudent to set out stringent guidelines concerning catheter insertion, irrigation and daily care, in an attempt to keep complications at a minimum. The role of intraductal yttrium, biliary endoprostheses and radiotherapy for these lesions in selected patients has yet to be determined.

While percutaneous transhepatic biliary drainage plays a beneficial role in some patients, its precise role in the treatment of malignant obstruction of the bile ducts remains to be defined.

Table IV—Benefits of Percutaneous Transhepatic Biliary Drainage

Symptoms/response	Hyperbilirubinemia	Pruritis	Anorexia
Present initially	23	19	21
Improved	18	8	5
No change	1	3	8
Not evaluable	4	8	8

Table V—Palliative Benefit of Biliary Drainage

Total duration of drainage, mo	No. of patients	Time at home, %*				
		0	< 25	25–50	51–75	> 75
< 1	8	7	1	–	–	–
1 – 4	5	3	–	–	1	1
> 4	8	–	1	1	2	4
Totals	21	10	2	1	3	5

*Time from drainage to death.

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BOOK REVIEWS

FLEXIBLE SIGMOIDOSCOPY. Ronald M. Katon, Emmet B. Keeffe and Clifford S. Melnyk. 158 pp. Illust. Grune & Stratton, Inc., Orlando, Fla., 1985. $34.50 (US). ISBN 0-8089-1701-3.

This complete manual presents even more than is necessary to learn the essentials of flexible sigmoidoscopy.

Eleven chapters cover all aspects of history, technique, indications and complications. Comparisons are made between the various brands of sigmoidoscopes, offering the physician who wishes to purchase a sigmoidoscope an objective means of making comparisons away from the persuasion of a salesman. Unfortunately, the newest endoscopes are not mentioned. The tip of the new instruments contains a microelectronic sensor that transmits an image to a television monitor; thus, the fiberoptic system is obviated. The cost of the new system is high, but maintenance will be much cheaper. The fiberoptic systems described in this book are all fragile, and the life of the fiberoptic system is the life of the entire sigmoidoscope.

The chapter on technique is the strongest one—by reading and following the instructions, the novice could become a self-taught sigmoidoscopist. The diagrams of the technique for sigmoidoscopy are most valuable. Words cannot express the value of the information provided by the line drawings illustrating the introduction and advancement of the sigmoidoscope. However, they go to far. If the sigmoidoscope is truly a screening tool, a discussion of electrocoagulation and electrosnaring is beyond the province of a diagnostic technique. Complete colonoscopy is almost always necessary whenever electrosurgery is indicated, and complete colon preparation makes electrosurgery safer with respect to explosion from hydrogen and methane. Furthermore, should a complication occur, the better-prepared bowel for colonoscopy will likely spare the patient a colostomy. Often a perforation in poorly prepared bowel will necessitate exteriorization of the perforation or proximal diversion.

The chapter on indications again brings the colonoscope into a conflict with the sigmoidoscope. Most doctors use the flexible sigmoidoscope as an office technique, specifically for screening asymptomatic patients. The moment the patient has blood in the stool, the finding of occult blood, a mass or a change in bowel habit, colonoscopy is required. Thus, the expense of a flexible sigmoidoscopy is avoided. To be cost-effective, duplication of diagnostic procedures must be prevented. Flexible sigmoidoscopy is not necessary if barium enema examination or colonoscopy is to be performed.

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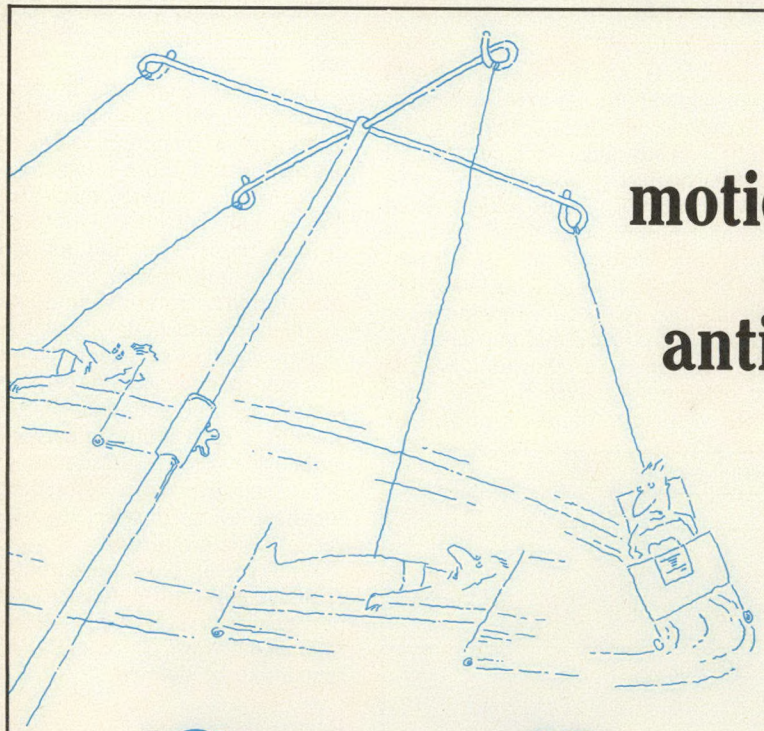

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Microbiologic Features and Treatment of Persistent Peritonitis in Patients in the Intensive Care Unit

The charts of 25 patients who died in the intensive care unit of persistent peritonitis after abdominal operations were reviewed to determine the microbial flora and the efficacy of antibiotic treatment. All patients had undergone two or more surgical procedures for abdominal sepsis and 23 had at least three-system organ failure. The most common organisms cultured were: *Staphylococcus epidermidis,* 24 cultures from 16 patients, *Candida albicans,* 19 cultures from 10 patients, *Pseudomonas aeruginosa,* 16 cultures from 12 patients, *Enterobacter,* 16 cultures from 8 patients and enterococcus, 14 cultures from 8 patients. The classic isolates, *Escherichia coli* (11 cultures from six patients) and *Bacteroides fragilis* (4 cultures from three patients) were found infrequently. To determine the adequacy of antimicrobial therapy for this "new" flora, we examined the ability of appropriate agents to eradicate the micro-organism upon subsequent culture. *Candida* sp. were eradicated in 54% (6 of 11) of the assessable cases, while enterococcus and *S. epidermidis* were cleared in only 25% and 28% respectively. The spectrum of intra-abdominal organisms cultured from critically ill surgical patients in the intensive care unit differs from that seen in those with acute peritonitis. Despite administration of appropriate antimicrobial agents, these organisms tend to persist, probably reflecting impaired host defences with multiple-system organ failure rather than antimicrobial failure.

On a étudié les dossiers médicaux de 25 patients qui sont décédés à l'unité des soins intensifs, des suites d'une péritonite persistante consécutive à une opération abdominale, dans le but de déterminer la nature de la flore microbienne et l'efficacité de l'antibiothérapie. Tous les patients avaient subi au moins deux interventions chirurgicales pour sepsie abdominale et 23 présentaient au moins trois insuffisances fonctionnelles. Les microorganismes les plus souvent cultivés ont été: *Staphylococcus epidermidis,* 24 cultures chez 16 patients, *Candida albicans,* 19 cultures chez 10 patients, *Pseudomonas aeruginosa,* 16 cultures chez 12 patients, *Enterobacter,* 16 cultures chez 8 patients, et l'entérocoque, 14 cultures chez 8 patients. Les isolats classiques, *Escherichia coli* (11 cultures chez six patients) et *Bacteroides fragilis* (4 cultures chez trois patients), ont été retrouvés plus rarement. Afin d'établir l'efficacité des traitements antimicrobiens sur cette "nouvelle" flore, on a étudié la capacité des antibiotiques appropriés à faire disparaître les microorganismes lors de cultures subséquentes. L'espèce *Candida* a été éliminé dans 54% (6 sur 11) des cas évaluables, alors que l'entérocoque et *S. epidermidis* disparaissaient dans seulement 25% et 28% des cas respectivement. Le spectre des microorganismes intra-abdominaux cultivés chez les patients chirurgicaux très malades alors qu'ils sont dans le service de soins intensifs diffère de celui qu'on retrouve dans les autres cas de péritonite. Malgré l'utilisation des antibiotiques appropriés, ces organismes ont tendance à persister, réflétant probablement de la sorte une atteinte des défenses immunitaires et une insuffisance multifonctionnelle, davantage que l'échec de l'antibiothérapie.

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The microbiologic chacteristics of peritonitis after perforation of the gastrointestinal tract are remarkably consistent.[1-3] The infections are usually polymicrobial and dominated by *Escherichia coli, Bacteroides fragilis,* streptococci (both aerobic and anaerobic) and eubacteria. Furthermore, blood cultures in these patients most often contain *B. fragilis* or *E. coli,* demonstrating the invasiveness of the micro-organisms.[1] The predictability of this flora has permitted the development of an empiric antimicrobial regimen used in conjunction with surgery in the treatment of peritonitis. Clinical and experimental studies have clearly demonstrated that antibiotics directed against both aerobic and anaerobic organisms should be given.[4,5]

The advent of intensive-care-unit (ICU) monitoring, total parenteral nutrition and broad-spectrum antibiotics have produced a subgroup of critically ill patients able to survive their initial abdominal procedure, but whose postoperative course is characterized by prolonged ICU care, multiple surgical procedures and the development of multiple-system organ failure. The death rate in these patients is high, ranging from 60% to 80%.[6,7] The microbiologic features and optimal antimicrobial therapy in such patients with persistent peritonitis is unclear. To clarify our impression that the bacterial spectrum of abdominal infection is radically altered during treatment, we reviewed the charts of patients who died in our surgical ICU of persistent intra-abdominal sepsis. The study revealed that the organisms cultured from these patients differed markedly from those found in patients who present with acute peritonitis.

Patients and Method

We reviewed the charts of 17 men and 8 women admitted over the 18-month period from July 1982 to December 1983 to the surgical ICU of the University of Minnesota Hospitals and who died with persistent intra-abdominal infection. Persistent peritonitis was deemed to be present in patients who required two or

more interventions (either operative or percutaneous drainage) for intra-abdominal sepsis.

In addition to standard demographic data, the review determined the microbiologic features of the intra-abdominal collections, the incidence of concurrent bacteremias and the ability of adequate antibiotic therapy to produce a microbiologic cure of the intra-abdominal infection. Adequate antibiotic therapy was defined as treatment with amphotericin B for *Candida* sp., ampicillin or vancomycin plus an aminoglycoside for enterococci and vancomycin for *Staphylococcus epidermidis* for at least 7 days. Cultures were taken for both aerobic and anaerobic bacteria. They did not represent cultures taken from drains in situ for a prolonged period, but rather cultures recovered either at reoperation or insertion of a fresh percutaneous drain.

Chart Findings

The mean age of the 25 patients studied was 61 years (range from 26 to 88 years). The initial operative site was small intestine (six patients), colon (four), biliary tract (four), pancreas (four), stomach (three), genitourinary tract (three) and peritoneum (one) for a necrotic infected intraperitoneal tumour. Two biliary tract procedures involved anastomoses to the small intestine (Whipple operation in one and choledochojejeunostomy in the other). One genitourinary procedure involved the formation of an ileal conduit followed by dehiscence of the small bowel anastomosis; another, a uretoureterostomy, was complicated by a postoperative sigmoid leak.

The average time between the initial operation and death was 55 days (range from 6 to 131 days). The average number of reoperations (or postoperative cutaneous drainages) was 3.1 (range from 1 to 8). Twenty-two patients received antibiotics effective against both facultative gram-negative bacilli and anaerobes.

Multiple-system organ failure during the course of the illness was frequent (92%) (Table I). In our ICU, during an overlapping period,[8] the need for dialysis was associated with a 6.3% survival rate while prolonged ventilatory support (7 days or longer) was similarly associated with a poor outcome (19.2% survival).

Table I—Multiple-System Organ Failure in Patients Dying of Persistent Peritonitis*

System failure	% of patients
Pulmonary (requiring ventilatory support)	80
Renal (dialysis required)	72
Central nervous system (decreased consciousness)	96
Hepatic (elevated bilirubin and alkaline phosphatase levels)	80
Cardiovascular (necessitating inotropic support, measurements indicating sepsis)	80

*Present during the course of the illness and not just pre-terminal events.

The microbial flora of persistent intra-abdominal infection is shown in Table II. These cultures were dominated (in decreasing order of frequency) by *S. epidermidis, Candida albicans, Pseudomonas aeruginosa, Enterobacter* and enterococcus while the classic microbial isolates (*E. coli* and *B. fragilis*) were less common.

The ability of an organism to produce a bacteremia is associated with its pathogenicity. To examine the invasiveness of this "new" flora, positive blood cultures were correlated with the presence of the bacteremic organism in the abdominal cultures. Twelve of the 25 patients had a total of 23 positive blood cultures during their postoperative course (or at autopsy in 2 patients). Three were polymicrobial and 20 monomicrobial. The common bacteremic organisms were *S. epidermidis* (nine), *Enterobacter* (four), enterococcus (three), *B. fragilis* (three) and *C. albicans* (three). In 18 of the 23 positive cultures, the bacteremic organism was present simultaneously in the peritoneal fluid culture, but not so in 3. The remaining two blood cultures had some, but not all, organisms present in the abdominal cultures. Of note, in the nine with *S. epidermidis* bacteremia, is that none had simultaneous positive cultures of central venous catheters. These results suggest that the intra-abdominal organisms demonstrated invasiveness by producing a bacteremia.

To assess the adequacy of antimicrobial therapy for the "new" flora in these critically ill patients, we examined the ability of appropriate agents to eradicate the micro-organism on subsequent cultures. These results are shown in Table III. Only amphotericin B, used to treat *Candida* sp. demonstrated at least moderate success (54%). Ampicillin and vancomycin were ineffectual in ridding enterococci from the cultures while *S. epidermidis* cleared equally well with or without antibiotics.

Discussion

At any given time the gastrointestinal tract contains more than 10^{12} bacterial organisms comprising over 400 species.[9] When the continuity of the tract is breached and bacteria are released, host defences eliminate most of these organisms. The resulting peritonitis contains a well-defined and consistent flora,[1-3] which is invariably polymicrobial, domi-

Table II—Microbiology of Persistent Peritonitis

Organisms	No. of positive cultures	No. of patients
Aerobes		
Staphylococcus epidermidis	24	16
Enterococcus	14	8
Alpha hemolytic streptococcus	4	3
Lactobacillus	1	1
Pseudomonas aeruginosa	16	12
Facultative gram-negative bacilli		
Escherichia coli	11	6
Klebsiella (pneumonia and *oxytoca)*	8	6
Enterobacter (cloacae and *aerogenes)*	16	8
Citrobacter freundii	1	1
Anaerobes		
Bacteroides fragilis	4	3
Clostridium (perfringens, clostridiformis and unidentified species)	5	3
Fusobacterium nucleatum	1	1
Corynebacterium sp	1	1
Fungus		
Candida albicans	19	10
C. glabrata	10	5
C. tropicalis	2	2
Aspergillus	1	1

Table III—The Ability of the Appropriate Antibiotic to Effect Microbiologic Cure

Organism	Patients assessable*	Appropriate therapy		Inappropriate therapy	
		No. of patients	Organism cleared	No. of patients	Organism cleared
Candida sp	14	11	6	3	0
S. epidermidis	12	4	1	8	4
Enterococcus	7	7	2	–	–

*Patients received at least 7 days therapy with the appropriate antimicrobial agent and a follow-up culture was available to assess efficacy of therapy.

nated by *E. coli*, enterococci, *B. fragilis*, anaerobic streptococci and eubacteria. The management of these infections is also well defined, combining surgical correction of the underlying disease with the administration of broad-spectrum antibiotics.[10] The need to provide antibiotic therapy, active against both aerobic and anaerobic bacteria, has been demonstrated, both experimentally and clinically.[4,5] Using a rat peritonitis model, Weinstein and colleagues[11] demonstrated a biphasic response to fecal contamination of the peritoneal cavity. This model closely mimics the clinical setting of bowel perforation in man. The first or peritonitis phase, was associated with a death rate of 40%. Bacteria recovered included mainly *E. coli,* enterococci and *B. fragilis.* The death rate correlated with the initial inoculum size of *E. coli.*[12] The survivors entered the second, or abscess phase, and were found to have abscesses at autopsy. The flora of these abscesses was dominated by the three bacteria just mentioned plus *Fusobacterium* sp. Gentamicin prevented death and clindamycin prevented abscess formation while the two drugs combined prevented both death and abscess formation.[5]

The findings from clinical studies corroborated these experimental findings. Thadepalli and colleagues[4] compared cephalothin and kanamycin to clindamycin and kanamycin in 100 patients with penetrating abdominal trauma. The aerobic infection rate was identical, but anaerobic infections developed in 11 of 52 patients treated with cephalothin and kanamycin versus 1 of 48 patients treated with clindamycin and kanamycin. Similarly, Berne and colleagues[13] showed that the combination of gentamicin and clindamycin in treating perforated appendicitis resulted in fewer septic complications than either cefamandole or cefoperazone alone, both cephalosporins with poor anti-anaerobic activity. Thus, the most favourable results in peritonitis are achieved when antibiotics are directed against both the aerobic (usually *E. coli*) and the anaerobic (usually *B. fragilis*) components.

Progress in metabolic and hemodynamic support in conjunction with conventional treatment has improved initial survival from peritonitis. However, these patients may subsequently manifest multiple-system organ failure. In the critically ill surgical patient, such failure is a predominant cause of late death after initial resuscitation.[14] We reviewed patients who died in our surgical ICU of persistent intra-abdominal infections to determine whether intensive therapy may have altered the microbial flora of these infections and also to see if appropriate adjustments of antimicrobial therapy could effect a microbiologic cure.

As expected, from a defined group of patients who died of sepsis in the surgical ICU, a high percentage (92.5%) had at least three-system organ failure during their clinical course. Studies from our institution[8] have shown that surgical ICU patients suffering renal or pulmonary failure have extremely high death rates (95% and 80% respectively). Fry and associates[15] demonstrated that patients with abdominal abscesses manifesting organ failure in three or more systems had greater than 80% mortality. They also showed that recurrent abscesses correlated significantly with an increasing likelihood of death.

The most frequently isolated organisms were *S. epidermidis, C. albicans, P. aeruginosa, Enterobacter* sp. and enterococcus. The classic microbial isolates, *E. coli* and *B. fragilis* were found much less frequently. Since almost all patients received broad-spectrum antibiotics, one would expect these relatively resistent micro-organisms to appear. The pathogenicity and origin of these organisms need to be considered.

The pathogenic roles of *P. aeruginosa* and *Enterobacter* sp. are above question and gram-negative bacteremias are associated with a 40% death rate.[16] *Pseudomonas aeruginosa* is one of the most frequently recovered organisms in the neutropenic bacteremic patient.[17] On the other hand, the virulence of *S. epidermidis,* enterococcus and *C. albicans,* especially when isolated from intra-abdominal sources, is not as clear.

Pathogenicity has been judged by the ability to cause bacteremia. Of the 25 patients in this study 48% had bacteremias (or candidemias) and cultures from these patients were dominated by *S. epidermidis, C. albicans* and enterococcus, indicating that these organisms have a propensity for invasion. Enterococcal bacteremias have been associated with death rates of 34% to 68%.[18–21] Dougherty and colleagues,[19] focusing on bacteremias originating from intra-abdominal sites, reported the highest death rate (68%). Their data also suggested that antienterococcal therapy may improve survival. Conversely, the data of Garrison and colleagues[20] demonstrated, as did our present study, that antibiotics specifically directed against enterococcus neither reduced the death rate nor effected cure. The death rate in patients with *S. epidermidis* bacteremia has ranged from 27% to 46%.[22,23] Burchard and colleagues[23] showed that specific antibiotic therapy reduced the death rate from 49% to 10%. In the patients in that study, central venous catheters represented the main focus of infection. We were unable to demonstrate a role for therapy directed against *S. epidermidis* in our patients. In fact, 50% of the bacteremias cleared without treatment. It is difficult to draw conclusions concerning the role of antimicrobial therapy against enterococcus and *S. epidermidis* isolated from intra-abdominal sites in these critically ill patients. We continue to administer drugs, based on the scanty evidence in the literature of their ability to reduce deaths and that enterococcemia may lead to enterococcal endocarditis.[19] We believe that these low virulence organisms represent markers, reflecting global depression of host immune defences in the critically ill patient but do not exert a specific pathogenicity.

The importance of *Candida* in intraperitoneal infections is better defined. Solomkin and colleagues[24] retrospectively reviewed 56 episodes of intraperitoneal infection in which various *Candida* sp. were identified. They showed the colonization of three or more sites with *Candida* predisposed to blood invasion. Furthermore, patients treated with amphotericin B, before candidemia, had a better survival rate than those not treated. They suggested that colonization of three sites was sufficient rationale for instituting amphotericin B therapy. In a subsequent paper[6] these same authors included 22 patients with organ failure in their assessment of antifungal therapy. They found that the survival rate was much lower (18%) in patients with organ failure before treatment than in patients without organ failure (78%). With such poor survival, it is difficult to justify antifungal therapy. The paper did not specifically examine the ability of amphotericin B to sterilize colonization sites in these critically ill patients. Our review suggests it is only moderately effective (54% sterilization) and that the risk of candidemia probably persists despite therapy.

It is interesting to speculate on the origin of the flora of these persistent intra-abdominal infections. In 9 of the 25 patients, there was a fistulous communication to the gastrointestinal tract or biliary system. In the remaining patients it is possible that the organisms recovered were residual organisms spilled at the initial episode of peritonitis and, by selective antibiotic therapy, they survived and ultimately infected the collection. Enterococci, *S. epidermidis* and *C. albicans* fall into the holes of antibiotic therapy. *P. aeruginosa* and *Enterobacter* sp. tend to be relatively antibiotic resistant. Evidence is increasing that these organisms originate from the gastrointestinal tract by the phenomenon of "bacterial translocation".[25] Wells and colleagues[26] showed that *B. fragilis* abscesses in rats attracted (and were ultimately colonized) by enterococci and *S. epidermidis* from the gastrointestinal tract. Stone and associates[27] observed *Candida* dissemina-

tion in dogs whose gastrointestinal tracts were inoculated with high doses of *Candida*. Bacterial translocation is encouraged by impairment of host cellular immune response.[28] The fact that this defect is present in patients with multiple-system organ failure supports this concept.[29] Further studies are needed to define the route by which bacteria (and yeast) leave the gastrointestinal tract to colonize sites of inflammation and produce systemic spread.

In summary, the microbial flora of critically ill patients with persistent intra-abdominal infection differs radically from that in patients admitted with acute peritonitis. It is dominated by organisms that tend to be multiple-antibiotic resistant and that individually are often considered low in virulence. Specific antimicrobial therapy, although still recommended, did not sterilize these cultures, probably reflecting impaired host defences in patients with multiple-system organ failure.

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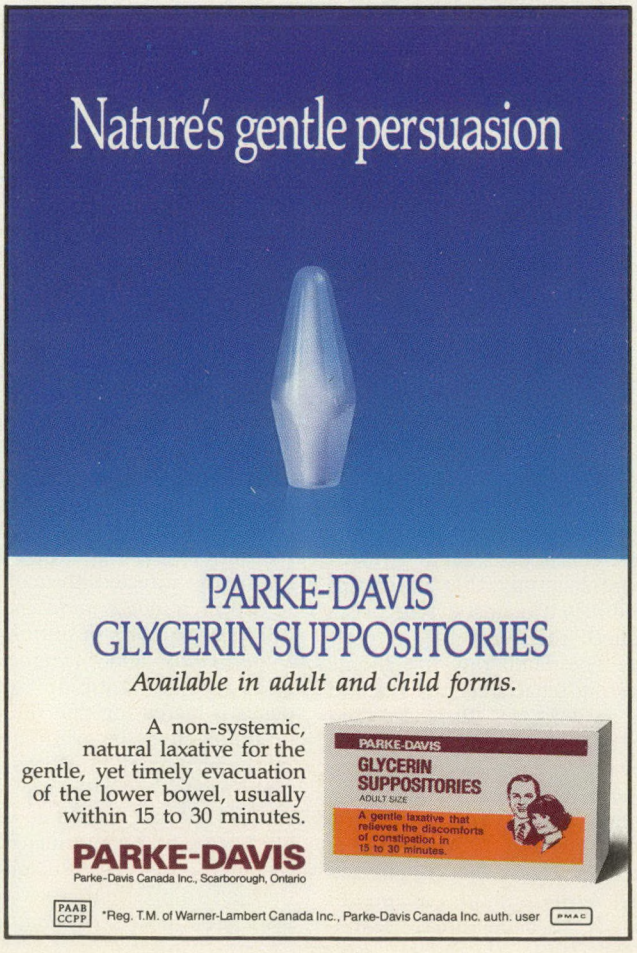

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JOSEPH G. SLADEN, MD, FRCSC

Presidential Address, 1985: Collecting

We are all collectors — collecting and organizing information being a very important part of medical practice. Viewing and collecting medical data are just the same as collecting stamps, and the personal computer has made it much easier for us. But we must get started, decide what to collect and how to display it. In vascular surgery, primary and secondary patency have been used to display results. In the author's opinion, the concept of actual palliation (a living patient with a patent graft) gives a much better reflection of what has actually been accomplished. In the "high-tech" future surgeons must know more about their collections than anyone else — or they will be directed by those who do. Let's accept the challenge now.

Nous sommes tous des collectionneurs puisque la collection et l'organisation de l'information constituent une partie importante de la pratique médicale. L'examen et la collection des données médicales s'apparentent à la collection de timbres et l'ordinateur personnel nous a rendu la tâche beaucoup plus facile. Il faut néanmoins se lancer, décider de ce qui sera collectionné et de quelle façon cela sera visualisé. En chirurgie vasculaire, la perméabilité primaire et secondaire a servi à visualiser nos résultats. Selon l'auteur, le concept de palliation (un patient vivant qui a une greffe perméable) illustre beaucoup mieux ce qui a été accompli. Dans un avenir où prévaudra la haute technologie nous devrons mieux connaître nos collections que quiconque; sinon, ceux qui sauront nous mèneront. Acceptons le défi. Dès maintenant.

To collect is defined in Webster's Dictionary as to gather together or assemble.

All of us collect — if only information for income tax! Any memorabilia or knick-knack can make a good collection and may be profitable. Most of us have collected stamps or coins to some degree. I still have all my Popular Mechanics and Lionel trains, collecting dust and my wife's wrath, and I'll bet most of you have your favourite old ski in the basement. These are a little like the old doctor with a series of one case — interesting but hardly a collection.

What is a collection? Unsoaked stamps have been saved, but they are definitely not a collection. Collections are organized, attractively displayed and have a common theme. The whole point of the collection is that it can be observed, enjoyed, refined and, if organized, understood.

In postgraduate training we collect a great deal of information. One of the important aims is to infuse the trainee with enthusiasm for adding in some way to medical knowledge or development. Two people, particularly, influenced me in this regard. Charles Rob had one of the most incisive minds I have ever encountered. There were hooks all over it, asking questions and looking for answers, collecting and organizing. Rounds were exciting. His surgery had the same precision and flair.

The second person was Professor Milnes Walker of Bristol who was a world authority on surgical control of portal hypertension. A humble and most gracious host, he had two sets of bar graphs displayed on his office walls; one showed patients after portacaval shunting and the other after transesophageal ligation of their varices. He extended the bar graph on each follow-up visit and coded "rebleeds", hepatic encephalopathy and death. The up-to-date results in his area of major interest were there for all to see: a brilliant surgeon and an academic collector.

Then, as now, treatment of femoropopliteal occlusive disease was a very hot topic. I first did a femoropopliteal vein graft in June 1964, and I have collected results of vein grafting procedures ever since. My collection was organized as bar graphs, and I marked revision with a line, occlusion with an X and death with a cross. I kept this on the wall of my office, soon covered by a curtain so that it didn't frighten patients. As the follow-up time increased the early cases looked a little like Flanders fields, with its crosses row on row!

Then the day of the main-frame computer was upon us. Henry Litherland recognized its value to the collector and developed a form to collect pertinent data associated with the surgery of occlusive vascular disease.[1] A year later Henry Hildebrand drew up a form for aneurysms. Using these forms we started a prospective study of vascular disease at St. Paul's Hospital in Vancouver in 1967, back loading my femoropopliteal collection at that time. There have been a few

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revisions in the last 18 years, one to improve collection of data on "redo" cases and the other, a format change to satisfy the "data punchers". The point is, that by making the decision to collect, we now have an organized prospective data base of patients, their surgical complications and subsequent operations since 1967. The fact that a few things have been changed has not been a real problem.

What To Collect

Several problems confront any collector and the most important is what to collect. In the field of stamp collecting, each collector makes decisions. Some collectors collect stamps from all over the world, but they are rarely able to sustain interest or input for such a wide collection. Even the stamp collector who specializes has decisions to make. Will he collect every existing ultra-rare stamp in his area? — a good "Penny Black" is worth $100 000.! Does it ruin the collection not to have it? A mistake I made was to stop collecting Canadian stamps prospectively about the end of World War II, they were just so common. Retrospective stamp collecting is a much more expensive exercise.

Without making tedium of the comparison, collecting medical data is no different. We must get started and decide what to collect; we can be satisfied with a data base that provides us with complete information on say 90% of the group as long as we can identify the missing information and find it. In writing up 100 cases, I would hope to pull no more than 15 charts and should go directly to them for one or two pieces of information. As numbers increase or interest focuses, new categories are necessary and a good data collection form has some leeway to accept them. Clearly, there is no need to look up all the vein grafts to pick out the in-situ grafts, so we changed a few numbers recently to identify them.

Storage and Access

The next problem confronting the collector is where to keep the collection and how to gain access to it. Valuable collections are often locked up in a bank vault, but active portions of the collection, where one is completing a page or adding to a contemporary area, must be available. Obtaining information from a mainframe computer through the interface of a programmer can be a little like borrowing money from a difficult banker, you may not get what you want! The great advantage of the personal computer is that it is interactive, which means that as you change an entry it is immediately visible on the screen or rejected with a discouraging beep. Linked mathematical changes are instantaneous. You can ask the computer what will happen if your next 10 patients fail or succeed. The interface between the collector and the personal computer is software. Good software programs are termed friendly. Compatible computers with friendly programs often lead to collectors being married to their computers.

Medical literature has become an overwhelming collection. Reports are being abstracted daily and are available to all of us on-line through a personal computer and modem. There is no question that this is the educational route of the future. The most up-to-date literature is available at one's finger tips the evening before a presentation or the arrival of a visiting professor. The microcomputer was refined for business purposes only 2 years ago and has become a fact of life in that short time.

FIG. 3—Big brother will be watching.

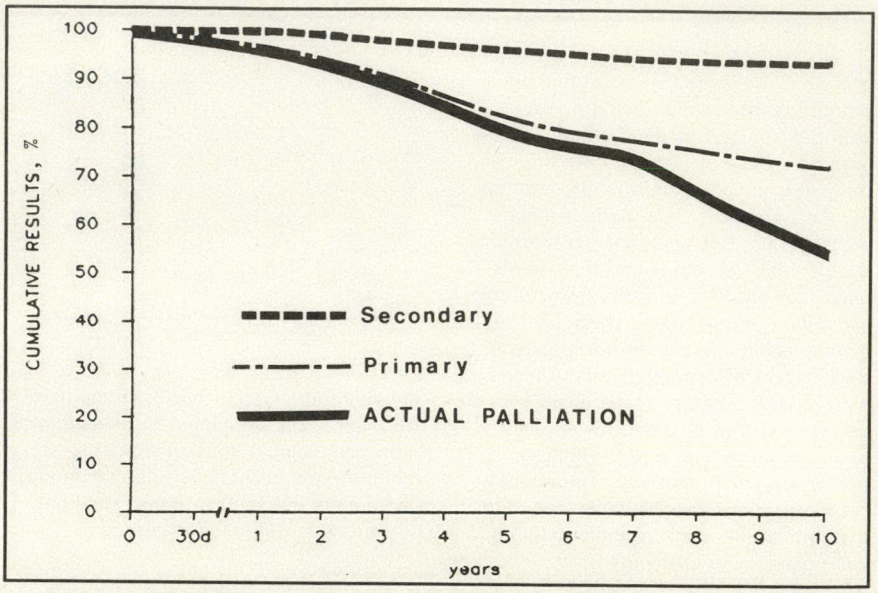

FIG. 1—Actual pallation curve (graft patent and patient alive) truly reflects patient benefit from operation.

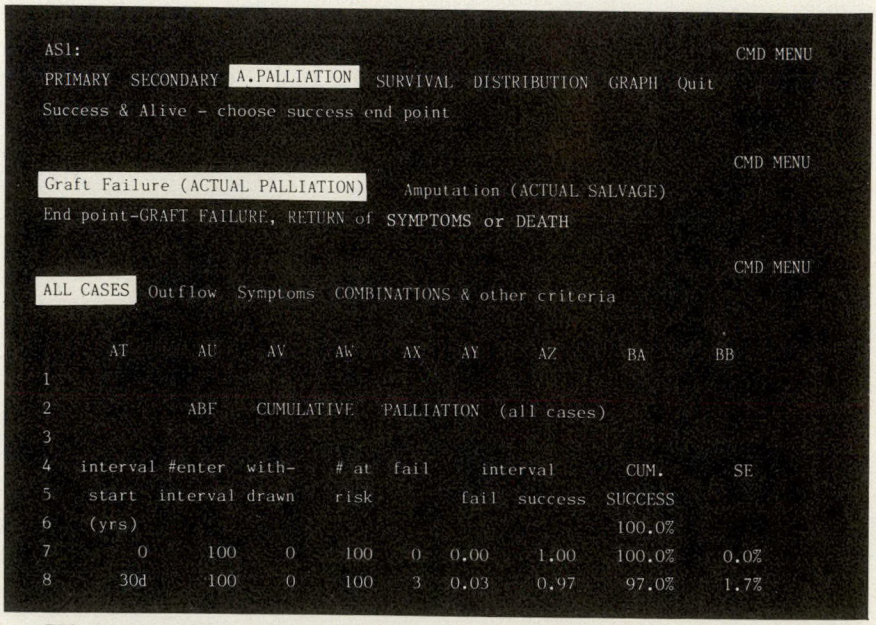

FIG. 2—Menu-driven software program to analyse patient data base on personal computer — the stamp album for the vascular collector.

Organization

The final problem is organizing the collection. The stamp collector buys an album with organized pages, ponders over the stamps and enters the best one. The more sophisticated collector divides the collection into mint and used or may have special interest in topics or cancels. The better and larger the collection, the more important is the organization and the display.

I have been particularly interested in displaying the results of medical collections. Much like stamps, our patients change as they progress through treatment. The patient who is being assessed is like the mint stamp; the patient after successful surgery, very fine used; after reoperation, socked on the nose; and treatment failure, faulty.

For our purpose in vascular surgery we can condense these phases into: primary, that is the durability of the original construction; secondary, our ability to keep it functioning with revisionary operations; and actual palliation, which we define as the combination of a successful graft and a living patient. With this display format for an aortofemoral collection, the results are informative and should influence future management (Fig. 1). They can be compared to results of femoropopliteal grafting for the same complaint.[2] It is difficult to say which curve is the most valuable, but in my opinion it is the actual palliation curve that best reflects patient benefit from the operation.

Over the last 2 years I have developed a menu-driven software program for the personal computer that analyses a patient data base and produces life tables and graphs under the above headings (Fig. 2). The end point for primary patency is usually revision or thrombectomy, but any late occurrence, reconstruction above or below, or false aneurysm, can qualify, depending on the study. Graft occlusion (failure) ends the secondary patency. Patient groups can be selected on the basis of outflow, symptoms, age, sex or any combination of factors the collector has entered. When combined with the data collection form, this is the stamp album for the vascular collector.

If we can define the exact criteria and aim of a study before we start, collecting can be very efficient. This was possible in the annual vascular surgery audit for which we decided to utilize only information that was easily retrievable in retrospect and to use hospital morbidity as the cut-off date, thereby eliminating long-term follow-up.[3]

Future

What does the future hold for medical collectors? Undoubtedly, we will all end up with computer access directly from our offices, whether it be a personal computer or a dumb terminal connected to a mini- or main-frame computer. Hospitals are gradually breaking down their computer fear. Medical records departments are great savers of questionable information. Perhaps through more direct input from medical personnel, we can identify what is important to us and delegate some of the leg work to those who are trained to do it.

Some collectors are born and others are made. In the "high-tech" future we are all involved and big brother will be watching (Fig. 3). It behooves us to know more about our collections than any one else, or we will be directed by those who do.

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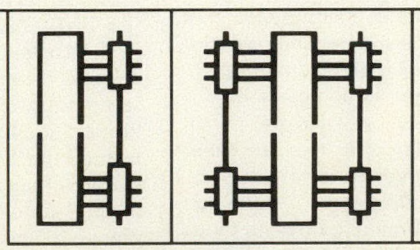

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JOHN A. MANNICK, MD, FACS

Edwards Foundation Lecture. Femoropopliteal and Infrapopliteal Reconstruction: State of the Art 1985

A review of recent reports in the surgical literature and the author's recent experience suggest that autogenous vein grafts remain the best method for arterial reconstruction below the inguinal ligament. The in-situ vein graft appears superior to reversed grafts for femoro-infrapopliteal reconstruction. Bypass grafts of polytetrafluoroethylene or human umbilical vein have not achieved satisfactory long-term patency even in the femoropopliteal position and should probably be used sparingly.

La revue des dernières communications dans la presse chirurgicale ainsi que l'expérience récente de l'auteur indiquent que la greffe de veine autogène demeure la meilleure technique de reconstruction artérielle sous le niveau du ligament inguinal. La greffe veineuse in situ paraît être supérieure à la greffe inversée dans les cas de reconstruction fémoro-infrapoplitée. Les dérivations à l'aide de tubulure de polytétrafluoroéthylène ou de veine ombilicale humaine n'ont su assurer une perméabilité satisfaisante à long terme, même en position fémoropoplitée, et doivent probablement être utilisées avec parcimonie.

Arterial reconstruction below the inguinal ligament, particularly that of the infrapopliteal vessels, remains a problem in vascular surgery. There is widespread agreement that the most effective means of treating femoropopliteal and femorotibial arterial occlusive disease is bypass grafting with autogenous vein. However, the late results of reversed saphenous vein grafting in the lower extremities have generally been inferior to those achieved with repair of occlusive disease of the aortoiliac system, the internal carotid arteries, the renal arteries, or the great vessels arising from the aortic arch.

The major cause of vein-graft failure is myointimal hyperplasia of the graft itself. Experimental evidence suggests that these lesions are the direct result of intimal injury, often occurring at the time the graft is harvested.[1] Recent work by LoGerfo and colleagues[2] indicated that careful handling of autogenous saphenous vein, when it is removed in preparation for grafting, coupled with the use of papaverine to prevent venous spasm, may reduce the incidence of intimal damage and subsequent hyperplastic lesions. Some clinical reports also suggest that careful handling of the vein may yield improved results for femoropopliteal and infrapopliteal vein grafts.[2,3]

In-Situ Grafting

There still remains the problem of size discrepancy using reversed saphenous vein, when the small distal end is attached proximally to the circumferentially larger and often thick wall of the common femoral artery. This situation frequently leads to a narrowing at the proximal anastomosis with damage to the intima distal to that point because of resulting flow disturbance and shear stress. This problem can be solved by the use of the saphenous vein in situ and, stimulated by the excellent results of the Albany group,[4] many surgeons have adopted the in-situ grafting technique with valve incision using instruments developed by Leather and associates.[5] The in-situ technique is also thought to cause less intimal damage to the vein because it is left in its natural bed and is perfused by arterial blood at physiologic pressure.

The early and intermediate results of the in-situ vein grafting technique in femoropopliteal and femoro-infrapopliteal reconstructions have been gratifying in our hands and in those of other surgical groups.[6,7] We found that the cumulative $2\frac{1}{2}$-year patency rate of femoropopliteal in-situ vein grafts was 82% in a series of 54 grafts and for femoro-infrapopliteal in-situ vein grafts 87% for a series of 47 grafts. These results are at least as good as those achieved on our service with the reversed saphenous vein graft in the femoropopliteal position and are superior to those in the femoro-infrapopliteal position.

The in-situ operation takes no longer to perform than reversed vein grafting and actually reduces the operating time for femoro-infrapopliteal bypasses in most instances. The technique has also increased our use of vein grafts. Previous experience indicated that the use of reversed autogenous vein grafts of less than 4 mm external diameter was accompanied by too high a graft failure rate to be worthwhile. However, the use of 3-mm diameter veins is feasible with the in-situ technique. This is probably because the larger end of the vein is anastomosed to the large common femoral artery and the smaller end to a small thinner-walled distal artery, and also because the incidence of myointimal hyperplasia in the vein graft itself is lower. For these reasons we believe that the in-situ vein graft is now the preferred method of arterial reconstruction below the inguinal ligament.

Polytetrafluoroethylene Grafts

Management of the patient who has limb-threatening ischemia and whose saphenous vein is either too diseased for use or has already been removed remains a problem. There has been widespread interest over the past decade in infrainguinal bypass grafts of polytetrafluoroethylene. The early enthusiasm for this material has been tempered considerably

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by the late results reported from a number of vascular surgical services.[8,9] Our experience suggests that bypasses of polytetrafluoroethylene grafts to the tibial vessels stay patent on the average for such a short period as to be contraindicated. The 5-year patency rate of 30% for 230 femoropopliteal polytetrafluoroethylene grafts is discouraging when compared with the results achieved using autogenous vein.

One problem with polytetrafluoroethylene grafts, in concert with other artificial prostheses crossing the knee joint, is buckling of the graft when the knee is flexed to 90° and beyond. Manufacturers have attempted to prevent this problem by incorporating external rings into the graft material. However, the grafts then appear to buckle the popliteal artery and failure rates, in our experience, have not lowered. Polytetrafluoroethylene grafts, both experimentally and clinically, are also associated with the development of a myointimal hyperplastic lesion at the distal anastomosis that appears to begin in the wall of the artery opposite the anastomotic suture line and to expand to involve the entire circumference of the artery and the lower portion of the graft itself.[10] The reason for this complication is not known, but it may be that the compliance mismatch between a stiff polytetrafluoroethylene tubing and a compliant host artery is responsible for damage to the arterial intima.

It has been suggested that the use of antiplatelet agents may improve the long-term patency of polytetrafluoroethylene grafts. The only experimental evidence supporting this concept is a report from Green and associates,[11] in which a small number of patients treated with antiplatelet agents were compared with those treated with placebo. It was found that only those patients with polytetrafluoroethylene grafts placed above the knee joint appeared to benefit from such therapy. A controlled double-blind study in which our service participated, failed to show improved patency of polytetrafluoroethylene grafts in patients treated with antiplatelet agents when compared with those treated with a placebo.[12]

In any event, the discouraging long-term patency rates of polytetrafluoroethylene in the infrainguinal position reported by a number of experienced surgeons suggest that grafts of this material should be used sparingly. The late results are similar to those reported in the early 1960s for Dacron prostheses in the infrainguinal region, and these grafts are now rarely used for femoropopliteal reconstruction.

There are reports suggesting that human umbilical vein may be superior to polytetrafluoroethylene for grafting in the femoropopliteal position.[9] We have been unable to duplicate these results on our service and have found that patency rates with umbilical vein are essentially the same as those with polytetrafluoroethylene. The umbilical vein graft is more difficult to use technically, is subject to unpredictable early failure, is very difficult to thrombectomize successfully, and is associated with late aneurysm formation.[13]

Alternatives

Since none of the artificial materials appear to be an alternative to autogenous vein grafts for femoral–distal popliteal and infrapopliteal reconstruction, a number of surgeons have turned to composite grafts for patients whose saphenous veins are unsuitable or missing. Conduits of polytetrafluoroethylene or Dacron above the knee are attached to shorter segments of autogenous vein to carry the graft below the knee joint. There is some evidence that composite grafts have a patency superior to that of artificial prostheses alone.[14,15] However, the Achilles' heel of a composite graft is the proximal prosthesis, which continues to have the disadvantages noted, even though it is attached distally to an autogenous venous graft. Our experience suggests that the results with composite are better than those of plastic prostheses alone when used below the knee. However, we believe that attaching the vein to the prosthesis by an end-to-end anastomosis should be avoided; this appears to result in buckling of the compliant vein by the non-compliant prosthesis with each pulse beat. A better technique is to anastomose each separately to a segment of popliteal artery above the knee joint if possible, or to use an end-to-side anastomosis of the vein to the prosthesis.

We believe an attempt should be made to use autogenous arm-vein grafts, which have been shown by several groups to have satisfactory long-term patency in the infrainguinal position, or composite venous grafts formed of arm vein and lesser saphenous vein, which is frequently ignored by vascular surgeons although it is usually intact and of adequate calibre. Use of such grafts, combined with proximal endarterectomy of the superficial femoral artery, will often permit satisfactory infrapopliteal reconstruction in patients whose saphenous veins have been removed or destroyed. There has been a rekindling of interest in the use of a more extensive endarterectomy of the superficial femoral and popliteal arteries, partly the result of a new motor-driven endarterectomy instrument that appears to do a better job than the old-fashioned loop strippers. The late results reported by one surgical group[16] using this technique, rival those achieved with autogenous venous grafts. At present, if at all possible, autogenous tissue reconstruction should be used below the inguinal ligament if a high late failure rate is to be avoided.

The Future

Hope should not be abandoned that a satisfactory small-vessel prosthesis will ultimately be developed. Modern techniques of endothelial cell culture, particularly recent advances in the purification and utilization of endothelial cell-growth factor, have opened the way towards the clonal expansion of endothelial cells harvested from short segments of autogenous vein for use in the lining of a prosthesis. Advances in polymer chemistry also suggest that the construction of an appropriately compliant prosthesis to accept an autogenous endothelial lining may be feasible in the near future. Perhaps an even more attractive idea is the growth in tissue culture of a totally autologous prosthesis composed of an endothelial-lined smooth-muscle tube, which has been found experimentally to be feasible if not commercially practical.

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K.C. GRANT, MD, FRCSC

Utility and Application of Pulmonary Artery Catheterization in Aortic and Aortoiliac Disease

To determine how useful pulmonary artery catheterization is in abdominal aortic surgery and which patients are most likely to benefit from the procedure, the author studied 28 patients with aneurysms and 22 with obstructive disease. Patients with multiple risk factors, except those with leaking aneurysms, were assessed before operation by pulmonary artery catheterization and volume loading (15 ml of 5% albumin/kg over 12 hours). All patients who underwent operation were assessed and monitored by pulmonary artery catheterization, beginning immediately postoperatively.

In 26 patients the procedure made a substantial contribution to assessment or care of their condition, not suggested by the usual clinical and technical modalities. In four patients the proposed surgery was affected; it was cancelled in one, delayed in two and replaced by a lesser procedure in one. Two other patients, thought to have unacceptable cardiac function, were considered suitable for operation after catheterization was done. Eleven patients with suboptimal cardiac index and 2 with volume overload were recognized early after surgery. Two patients with oliguria following repair of a ruptured aneurysm had optimal cardiac indices and renal perfusion assured by pulmonary artery catheterization, which helped to identify unsuspected pulmonary hypertension in three patients, bleeding in one and intestinal infarction in one.

Twenty-seven patients were challenged before surgery with 5% albumin and their response was analysed. In 7 there was no response to the colloid challenge and they suffered much more morbidity than the 20 patients who had a positive hemodynamic response to challenge.

Multiple regression analysis of disease and risk factors among the 50 patients showed that age and cardiac status were independent and were the most dominant of all variables in determining the likelihood of benefit from pulmonary artery catheterization.

Dans le but de déterminer l'utilité du cathétérisme de l'artère pulmonaire dans la chirurgie de l'aorte abdominale et d'identifier les patients les plus susceptibles de bénéficier de cette intervention, l'auteur a étudié 28 patients souffrant d'anévrisme et 22 de maladie occlusive. Les patients présentant des facteurs de risque multiples, à l'exception de ceux qui avaient un anévrisme suintant, ont été évalué avant l'opération par cathétérisme de l'artère pulmonaire et charge de volume (15 ml d'albumine à 5%/kg sur une période de 12 heures). Tous les patients qui ont subi l'opération ont été évalués et surveillés par cathétérisme de l'artère pulmonaire en commençant dès la fin de l'intervention.

Chez 26 patients, l'intervention a contribué de façon importante à l'évaluation des soins apportés à leur état, contribution que n'auraient pu apporter les moyens cliniques et techniques habituels. Dans quatre cas, l'opération envisagée a été modifiée; une chirurgie a été annulée, deux ont été retardées et une a été remplacée par une intervention réduite. Deux patients que l'on croyait inaptes à l'opération en raison d'une insuffisance de la fonction cardiaque se sont qualifiés au cathétérisme, Onze patients ayant un index cardiaque sous-optimal et deux ayant une surcharge de volume ont été identifiés peu après l'opération. Deux patients présentant une oligurie après réparation d'un anévrisme rupturé ont montré au cathétérisme de l'artère pulmonaire, un index cardiaque optimal et une bonne perfusion rénale; ceci a permis d'identifier une hypertension pulmonaire insoupçonnée chez trois patients, du saignement chez un et un infarctus intestinal chez un autre.

Avant l'opération, 27 patients ont été mis à l'épreuve à l'aide d'albumine à 5% et leur réponse a été analysée. Sept d'entre-eux n'ont pas réagi à cette épreuve au colloïde; on a constaté chez eux une morbidité beaucoup plus considérable que chez les 20 qui ont répondu positivement à l'épreuve hémodynamique.

Chez 50 malades, une analyse de régression multiple portant sur la maladie et les facteurs de risque a montré que l'âge et l'état de la fonction cardiaque étaient indépendants; de toutes les variables, elles étaient les plus importantes pour déterminer la probabilité de bénéficier d'un cathétérisme de l'artère pulmonaire.

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The role of invasive hemodynamic monitoring in patients who undergo major vascular surgery remains controversial. These patients tend to be elderly, many have critical vascular disease in other areas and many have chronic lung disease. The basic monitors of pulse rate, blood pressure and urinary excretion rate in patients who undergo surgery are often unreliable in the patient with aortic-vascular disease, as a result of preoperative beta blockade, aortic clamping and operative diuretic therapy. Central venous pressure is not a reliable monitor of the rapid changes that may take place and is often misleading, especially in the presence of pulmonary artery hypertension. On the other hand, pulmonary artery catheterization adds complexity to the care of the aortic surgical patient and is associated with a morbidity of its own.[1]

This study was undertaken to determine how useful pulmonary artery catheterization is in aortic surgery, the nature

of the benefits, and to see if patients deriving benefit could be identified.

Methods

Fifty consecutive patients, 28 with aneurysmal disease and 22 with obstruction, were assessed by pulmonary artery catheterization. Patients (33 of the 50) with multiple clinical risk factors, excluding those with ruptured aneurysms, underwent baseline studies preoperatively. Twenty-seven of this group were challenged with 5% albumin solution (15 ml/kg over 12 hours) to evaluate cardiac performance and optimize preload before operation. All who had direct aortic surgery (48 patients) were assessed immediately after by pulmonary artery catheterization and monitored for at least 48 hours.

As each patient was assessed and treated, the substantial contributions made by catheterization to the assessment or care of that patient, not indicated by other clinical or technical modalities, were noted prospectively and classified accordingly as major (3), intermediate (2) or minor (1).

After identifying patients in whom catheterization was considered useful, our group developed a statistical model that included individual variables, to see if we could identify those patients likely to derive benefit from pulmonary artery catheterization. The variables included age, sex, cardiac status (New York Heart Association, 1973[2]), clinical risk factors of renal, cerebral, respiratory and metabolic origin, and the presence preoperatively of hypertension; these were considered together with the nature of the disease treated, obstructive or aneurysmal.

Apart from benefits in individual patient care, the initial preoperative information obtained from catheterization, with the response to challenge with 5% albumin, was examined to see if outcome and morbidity were predictable by that initial assessment.

Results

Usefulness of Pulmonary Artery Catheterization

In 26 of 50 patients the procedure made substantial contributions to assessment or patient care (Table I). These were major in 10 cases, intermediate in 7 and minor in 9.

Cancellation of surgery.—A 74-year-old man with chronic obstructive pulmonary disease, aortoiliac obstruction and ascending aortic aneurysm had his surgery cancelled because the catheterization indices deteriorated after challenge with 5% albumin.

Alteration of a planned procedure.—In one 70-year-old man with an ascending aortic aneurysm whose catheterization indices deteriorated following challenge with 5% albumin, the aneurysm surgery was cancelled and axillobifemoral grafting carried out 6 days later.

Delay of surgery.—Two patients whose initial assessment revealed marginal cardiac indices and elevated pulmonary capillary wedge pressures had their operations postponed. Digitalis was prescribed and 7 days later when their condition was improved the aortic operations were performed.

Upgrading of fitness assessment.—Two patients were considered poor candidates for aortic surgery by medical assessment. Following pulmonary artery catheterization and a good response to 5% albumin challenge they were considered to be at less risk and they subsequently underwent uncomplicated aortic surgery.

Optimal cardiac index and renal insufficiency.—Two patients had persistent oliguria after repair of ruptured abdominal aneurysms. Optimal renal perfusion was assured by pulmonary artery catheterization in circumstances in which overload and adult respiratory distress syndrome were potential hazards.

Recognition of volume/preload deficiency.—In three patients volume deficiencies were recognized postoperatively by pulmonary artery catheterization, but the information obtained from basic monitoring was within the normal range. These patients required an average of 630 ml of red blood cells and plasma to restore normal catheterization indices. Twenty-seven patients had moderate hypertension early after operation; in 8 of them, relative volume/preload deficiency was exposed after vasodilator therapy for increased systemic vascular resistance—an average of 890 ml of red blood cells and plasma corrected the abnormality with return to normal indices. The volume deficiencies in these patients, in the absence of pulmonary artery catheterization data, might not be evident until renal recovery from operative diuretic therapy and oliguria occurred.

Volume overload.—Two patients who suffered interstitial pulmonary edema and had evidence of respiratory failure after aortic surgery were found by catheterization to have volume overload. The clinical distinction between respiratory failure, pneumonia and adult respiratory distress syndrome may be difficult without pulmonary artery catheterization.[3]

Pulmonary artery hypertension.—Three patients had serious pulmonary artery hypertension, with systolic pressures over 35 mm Hg. Lesser degrees of pulmonary artery hypertension were frequent. Those with severe hypertension are at special risk because they are more sensitive to volume overload and have an increased susceptibility to adult respiratory distress syndrome; in some instances pulmonary hypertension can impair left ventricular performance.[4,5]

Early recognition of bleeding.—A 69-year-old man with infrarenal aortic obstruction and renal artery stenosis had hypertension, treated with β-blockers. Two hours after repair of the obstructed abdominal aneurysm and aortorenal bypass, pulmonary artery hypotension developed and there was a drop in cardiac index without systemic hypotension. With volume infusion, the catheterization indices returned to normal, but after 1 hour the previous abnormal indices of pulmonary artery catheterization were again noted. The patient was returned to the operating room and suture-line bleeding controlled. At no time did the patient manifest systemic hypotension, tachycardia or a decrease in urine volume. Pulmonary artery catheterization in this instance served as an early warning system.

Intestinal ischemia.—As a result of a hemodynamic failure of a cross-femoral graft a 74-year-old man underwent operation for aortoiliac obstruction. He had coronary artery disease and had had a myocardial infarction. At operation, in

Table I—Contribution of Pulmonary Artery Catheterization to Individual Care of 50 Patients with Aortic Aneurysms or Obstruction

Contribution	No. of patients	Weighting*
Cancellation of surgery	1	3
Replacement by lesser operation	1	3
Delay of operation	2	3 x 2
Upgrading of fitness assessment	2	1 x 2
Assurance of optimal cardiac index in oliguric patients	2	2,3
Recognition of:		
Volume/preload deficiency with hypertension	11	1 x 5, 2 x 4, 3 x 2
Volume overload	2	2 x 2
Pulmonary artery hypertension	3	3 x 3
Postoperative bleeding	1	1
Intestinal infarction	1	1

*1 = minor benefit, 2 = intermediate benefit, 3 = major benefit.

addition to aortobifemoral grafting, a stricture of his small intestine was resected. Forty-eight hours later he became hypotensive and tachycardiac. His cardiac index (6.3) on pulmonary artery catheterization was double that of the early postoperative value (3.1), his systemic vascular resistance index had dropped from 1065 to 878 and his arteriovenous oxygen difference was 2. At laparotomy total colectomy was required for colonic infarction. In a patient such as this who is still on the respirator and heavily sedated 48 hours after operation, other causes of hypotension, cardiac- or volume-related, would be difficult to exclude without pulmonary artery catheterization.

Colloid Challenge with 5% Albumin: Relationship to Outcome

In addition to the individual contributions by pulmonary artery catheterization to patient assessment and care, the relationship between the response to challenge by 5% albumin to outcome after operation was examined. The 27 patients challenged by 5% albumin who subsequently had aortic surgery responded in one of two ways. In 20 patients (group 1), the mean cardiac indices increased (from 2.93 ± 0.4 ml/min•m^{-2} to 3.6 ± 0.62 ml/min•m^{-2}); in the other 7 patients (group 2) cardiac indices did not increase (3.18 ± 0.21 ml/min•m^{-2} versus 2.98 ± 0.3 ml/min•m^{-2}). In Fig. 1 the net change in cardiac index is shown for each patient together with the mean change and standard deviation for all 27 patients. The cardiac index in all group 2 patients fell below one standard deviation from the mean.

Outcome.—In group 1 patients there was major morbidity in two but no deaths (Fig. 2). One patient required reoperation for bleeding and the other a colectomy for intestinal ischemia. In group 2, there was major morbidity in four patients. One patient had cardiac arrest in the operating room and a second experienced ventricular fibrillation in the intensive care unit shortly after surgery. A third patient had recurring cardiac failure and died at home 60 days after operation. A fourth suffered from adult respiratory distress syndrome and sequential organ failure and died 14 days after operation. This was the only death in the series in electively treated patients.

Characterization of Patients Deriving Benefit From Pulmonary Artery Catheterization

From initial overview of our 50 patients, those with aneurysms (8 of 22) and obstruction with multiple risk factors (8 of 22) appeared more likely to benefit from pulmonary artery catheterization.

However, when benefit was quantified (from 1 to 3) and interacting terms were examined by multiple regression analysis, the common features were those of age and cardiac status as independent and dominant variables in the models. The R^2 in this analysis was 50.84.

When unruptured aortic aneurysms and obstructions were examined, both separately and together, the variables became part of a more homogeneous pattern with higher R^2 values, from 63 to 70; again age and cardiac status appeared as the dominating factors.

Since pulmonary artery catheterization is essentially a cardiac assessment, a further model was constructed interacting cardiac status with all other variables. The stepwise regression process again showed age and its interaction with cardiac status to be the important variables. The formula in Fig. 2 characterizes precisely (with $R^2 = 50.17$) those patients deriving benefit from pulmonary artery catheterization and the degree of benefit they might expect.

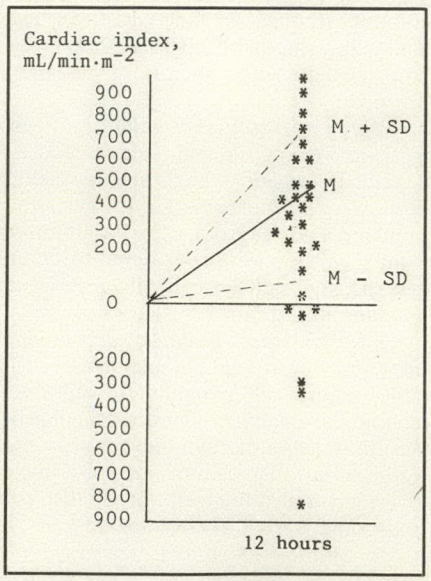

FIG. 1—Response to 5% albumin challenge over 12 hours. Mean increase in cardiac index was 390 ± 300 ml/min•m^{-2}. All patients in group 2 are below one standard deviation from mean.

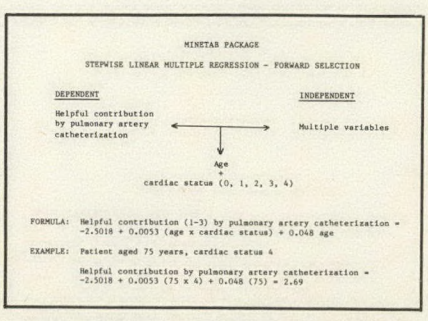

FIG. 2—Characterization of group deriving benefit from pulmonary artery catheterization.

Discussion

In our group of patients who required abdominal aortic surgery, pulmonary artery catheterization was frequently beneficial, especially for elderly patients with cardiac impairment. In studies of survivors of critical illness, it has been shown that those with the capacity to provide above-normal performance ("optimal goals versus normal values") with respect to cardiac index, oxygen delivery and other indices, are more likely to survive.[6,7] It may be that those who cannot improve their cardiac performance substantially above a resting baseline level are poor candidates for major aortic surgery. They could be identified by constructing cardiac performance curves, but this is difficult, time-consuming and is only valid if end-diastolic volumes are measured.[8] Observing cardiac response, by pulmonary artery catheterization, to a standard colloid challenge may be more practical and simple.

In older patients with cardiac impairment who are candidates for aortic surgery, assessment and monitoring by pulmonary artery catheterization will frequently be of benefit and should help to minimize the increased morbidity and mortality of that group.

I would like to thank Dr. Harry Love, Chairman, Department of Mathematics, University of Prince Edward Island, for his assistance in the analysis of material presented in this paper. I also thank Mr. Merril Smith of the Audiovisual Department, Queen Elizabeth Hospital for his assistance in preparing the graphs and photographs.

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Low-Dose Intra-arterial Streptokinase Infusion Therapy of Peripheral Arterial Occlusions and Occluded Vein Grafts

To study the effectiveness of low-dose thrombolytic therapy the authors report their experience with local, low-dose, intra-arterial streptokinase infused at a rate of 5000 units/h in four patients with occluded vein grafts and eight with peripheral arterial occlusions presenting with limb-threatening ischemia. The patients had had symptoms for 4 hours to 6 weeks. The streptokinase infusion successfully declotted two occluded vein grafts and restored distal blood flow in five patients with peripheral arterial occlusion. Complications resulting in early withdrawal of thrombolytic therapy included surgical wound hematomas in two patients. Two patients had severe bleeding at the arterial puncture site leading to the death of one of them. Treatment after cessation of thrombolytic therapy included femoropopliteal bypass in three patients, percutaneous transluminal balloon dilatation of a stenotic popliteal artery in one patient and thromboembolectomy in three patients. Two patients required below-knee amputation because of irreversible ischemia.

The authors conclude that in carefully selected patients, intra-arterial infusion of streptokinase locally in low dosage is an important adjunct in the treatment of limb-threatening ischemia caused by occluded vein grafts and acute arterial thrombosis. They warn that selective thrombolytic therapy with streptokinase must be used with caution since it may be associated with serious complications.

On décrit les résultats d'une étude sur l'efficacité d'un traitement thrombolytique par perfusion locale intra-artérielle de streptokinase à faible dose. Le produit a été administré à raison de 5000 unités/h chez quatre patients ayant une occlusion de greffe veineuse et chez huit souffrant d'occlusion artérielle périphérique qui ont été vus pour une ischémie susceptible d'entraîner la perte d'un membre. Les symptômes étaient présents depuis des périodes allant de 4 heures à 6 semaines. La perfusion de streptokinase a permis de dissoudre le caillot dans deux cas d'occlusion de greffe veineuse et a rétabli la circulation sanguine distale chez cinq patients souffrant d'occlusion artérielle périphérique. Chez deux patients, un hématome au point d'incision a entraîné l'arrêt précoce du traitement thrombolytique. Deux autres patients ont eu une hémorragie importante au point de piqûre artérielle, ce qui a causé la mort de l'un des deux. A l'arrêt de la thérapie thrombolytique, le traitement s'est poursuivi par pontage fémoropoplité chez trois patients, dilatation transluminale percutanée par ballonnet dans un cas de sténose de l'artère poplitée et thromboembolectomie dans trois cas. Deux patients ont dû subir une amputation en dessous du genou à cause d'une ischémie irréversible.

Les auteurs concluent que chez des patients soigneusement choisis, la perfusion locale intra-artérielle de streptokinase à faible dose contribue de façon importante au traitement de l'ischémie causée par l'occlusion d'une greffe veineuse ou par thrombose artérielle aiguë, mettant en péril la survie du membre. Ils mettent en garde contre l'utilisation sans précaution du traitement thrombolytique sélectif à la streptokinase, car celui-ci peut être relié à des complications sérieuses.

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The effectiveness of regional administration of thrombolytic agents at low dosage to treat peripheral arterial occlusions has been confirmed by reports of several authors.[1-8] Hargrove and associates[9] reported successful recanalization of totally occluded femoropopliteal vein grafts in four patients receiving low-dose streptokinase infusion. Current concepts and guidelines for the use of thrombolytic agents are well established and have been reviewed in detail by Bell and Meek.[10] We evaluated this treatment in 12 patients with limb-threatening ischemia, considered ideal candidates for local, low-dose, thrombolytic therapy.

Patients and Method

Four patients with occluded femoropopliteal vein grafts and eight with arterial occlusions were treated with local, low-dose, streptokinase infusion at the Health Sciences Centre in Winnipeg between September 1982 and March 1985.

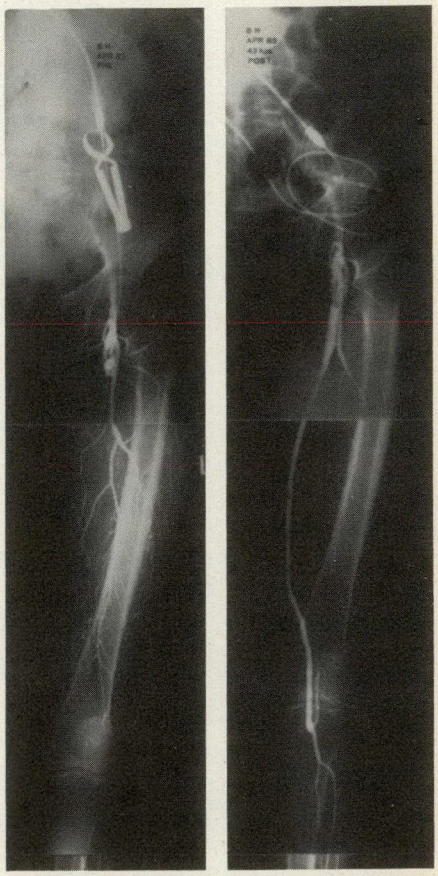

FIG. 1—Preoperative angiogram of occluded left femoropopliteal vein graft (left). Completely declotted vein graft after 43 hours of intra-arterial streptokinase infusion (right).

Of the 12 patients, 8 were men and 4 women, ranging in age from 52 to 80 years. All had acute limb-threatening ischemia. The duration of symptoms ranged from 4 hours to 6 weeks. Screening eliminated any contraindications to thrombolytic therapy.

Coagulation studies, including platelet count, thrombin, prothrombin and partial thromboplastin times were measured before, during and after therapy. Transfemoral angiography identified the sites of occlusion, except in one patient in whom a transaxillary approach was used.

After the site of occlusion had been visualized angiographically, a no. 4 or 5 French angiographic catheter was placed through the same arterial puncture site, under fluoroscopic control, as close to the thrombus as possible to deliver the maximum concentration of streptokinase to the site of thrombosis. Streptokinase was administered at a rate of 5000 units/h for up to 72 hours. To avoid catheter thrombosis, we found that dilution of streptokinase to 1000 units/ml with normal saline by way of a sage pump was most satisfactory. Vital signs and arterial puncture sites were monitored in the intensive care unit. Coagulation studies were performed every 12 hours and when necessary.

Patients were assessed frequently by Doppler and pressure measurements. Follow-up arteriographic studies were performed 24 to 72 hours from the onset of therapy. Moderate arterial lesions remaining after therapy were treated by direct surgery or transluminal angioplasty.

When streptokinase infusion was successful the patient was placed on heparin followed by oral anticoagulation for 3 to 6 months.

The following three case reports illustrate the typical course of patients with arterial lesions and occluded vein grafts treated by streptokinase infusion.

Case Reports

Case 1

A 68-year-old woman had a 10-hour history of acute pain in the left leg.

Thirty-two months earlier, because of rest pain, she had undergone femoropopliteal bypass grafting below the knee, using reversed saphenous vein and proximal superficial placement of a femoral artery onlay patch to the left common femoral artery.

Physical examination revealed a pale, cool, left leg with a 4+ femoral pulse but no palpable distal pulses. Motor and sensory functions were intact. Arterial flow at the ankle was undetectable by Doppler. Left transfemoral arteriography, performed immediately after admission, demonstrated complete occlusion of the left femoropopliteal bypass graft with a patent common femoral artery (Fig. 1). A no. 5 French infusion catheter was inserted through the same arterial puncture site by means of a guide wire and the catheter tip advanced approximately 3 cm into the occluded femoropopliteal vein graft under fluoroscopic control.

A continuous infusion of streptokinase at 5000 units/h produced complete lysis of the clot in 43 hours with resumption of good flow (Fig. 1).

No lesion requiring surgical correction was demonstrated on the follow-up arteriograms. Coumadin was prescribed and at the time of discharge the ankle pressure was 92 mm Hg with a brachial pressure of 160/90 mm Hg.

The graft became occluded again after 15 months and was treated successfully with streptokinase infusion. The graft has remained patent for the past 14 months.

Case 2

A 62-year-old white man presented at a local hospital with rest pain of sudden onset in the

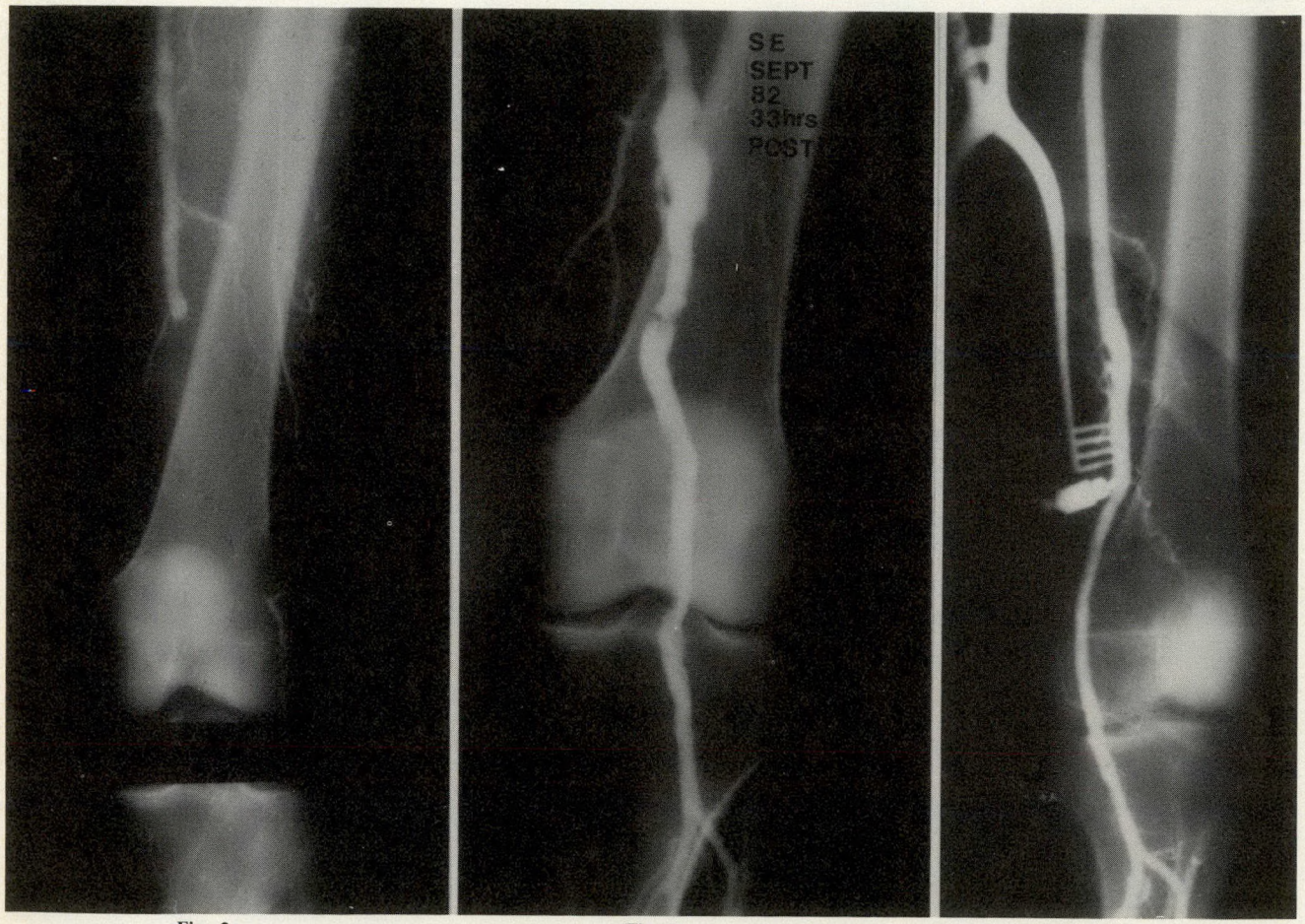

Fig. 2a Fig. 2b Fig. 2c

FIG. 2—(a) Angiogram of occluded distal superficial femoral artery and interposition vein graft. (b) Angiogram 33 hours after streptokinase therapy shows completely declotted occluded segment but aneurysmal dilatation of distal superficial femoral artery. (c) Angiogram at end of operation showing reconstruction with polytetrafluoroethylene interposition graft.

left leg. He was treated with heparin intravenously for 3 days before transfer to the Health Sciences Centre in Winnipeg.

The patient had undergone bilateral popliteal aneurysm resections and interposition grafting with reversed saphenous vein, 9 and 6 years earlier respectively. Aortoiliac bifurcation grafting had been performed 3 years before when an abdominal aortic aneurysm was resected. He had been a smoker for many years and had suffered myocardial infarction 2 months before admission.

On examination the left leg was pale and cool with intact motor and sensory functions. There was 4+ femoral pulse but no palpable distal pulses. A left transfemoral arteriogram demonstrated both a distal superficial femoral artery and interposition vein-graft occlusion (Fig. 2a).

A no. 4 French intra-arterial infusion catheter was placed, under fluoroscopic control, proximal to the occlusion site and a continuous intra-arterial streptokinase infusion (5000 units/h) begun. The saphenous vein interposition graft was completely declotted after 33 hours of continuous infusion. In the follow-up post-infusion arteriogram there was a proximal aneurysm in the superficial femoral artery and stenosis at the proximal anastomosis (Fig. 2b). An interposition polytetrafluoroethylene graft was placed to correct the lesion (Fig. 2c).

Postoperatively, the patient had good, palpable, pedal pulses, and his ankle pressure was 110 mm Hg with a brachial pressure of 129/79 mm Hg.

Coumadin therapy was prescribed, and at follow-up 11 months later the graft was still patent.

Case 3

A 71-year-old white man experienced sudden onset of rest pain in his left leg. A left transfemoral angiogram (Fig. 3a) revealed proximal occlusion of the left popliteal artery. He was transferred to the Health Sciences Centre 3 weeks later.

His relevant medical history included chronic hypertension, renal insufficiency, cardiac arrhythmia and a myocardial infarction suffered 4 years earlier. Physical examination revealed a pale, cool, left leg with intact motor function and decreased sensation. There was a normal femoral pulse but no distal pulses.

A no. 4 French infusion catheter was inserted by the transfemoral route on the same side and its tip advanced under fluoroscopic control to the occlusion site. A continuous intra-arterial infusion of streptokinase (5000 units/h) opened the popliteal artery and distal vessel, all the way to ankle and foot, in 48 hours (Fig. 3b).

After the infusion, ankle pressure was 140 mm Hg with a brachial pressure of 175/95 mm Hg. The patient was discharged on coumadin therapy and 33 months postoperatively the left limb vessels were patent.

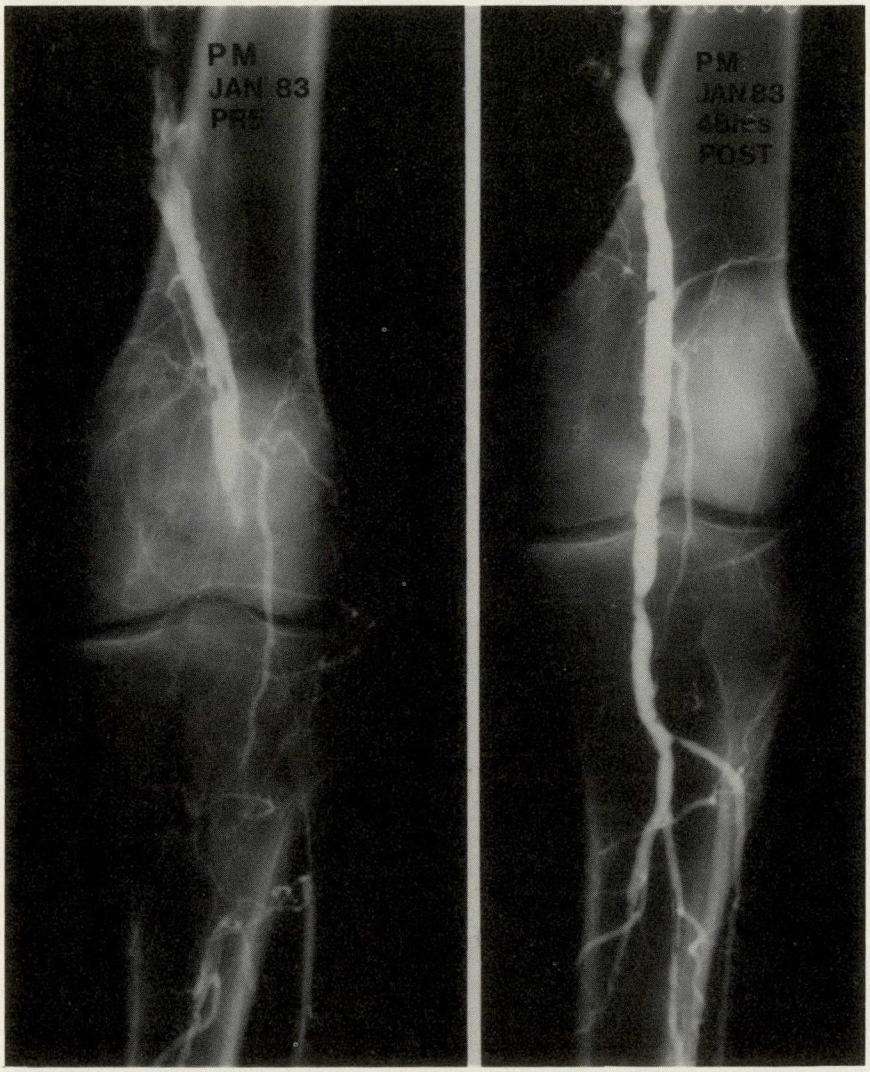

Fig. 3a

Fig. 3b

FIG. 3—(a) Angiogram of occluded left popliteal artery. (b) Patent popliteal artery after 48 hours of intra-arterial streptokinase infusion therapy.

Results

In six of seven patients (Table I) thrombolytic therapy was successful, the arteries were patent and the limbs preserved. One patient (no. 7) required below-knee amputation owing to distal thrombosis, even though proximal lysis was obtained. In four patients streptokinase was discontinued because of hematoma formation. Two large retroperitoneal hematomas arose from the angiography puncture site above the inguinal ligament and one patient died as a result.

Discussion

Streptokinase is a product of β-hemolytic streptococci, group C, and produces clot lysis by activating the human fibrinolytic system.[11] It combines with the inactive proenzyme plasminogen to form an activator complex that in turn enzymatically converts available plasminogen to plasmin, the active fibrinolytic enzyme.[12] Streptokinase has two half-lives: the first is 18 minutes and represents clearance after binding with antistreptokinase antibodies, and the second is 83 minutes.

Operative intervention in late occlusion of vein grafts has often been unsatisfactory because of difficult thrombectomy or the presence preoperatively of unidentified lesions such as a valve cusp stenosis.[13] Lysis of the clot is less traumatic than thrombectomy and a lesion precipitating the occlusion may be identified. In one patient with a vein graft there was no demonstrable cause for graft occlusion after lysis had been accomplished. In five patients with arterial occlusions, lysis of the clot permitted identification of lesions such as arterial stenosis and aneurysm as causes of acute arterial thrombosis that were treated successfully by surgical reconstruction or balloon dilatation. When arterial thrombosis occurs with severe distal disease, lytic therapy may be preferable to surgery. However, infusion time required for complete lysis may be up to 72 hours so if ischemia is severe, limb viability may preclude lytic therapy. If there is good motor function and only minor sensory deficit in the limb, lytic therapy may be initiated under close observation. It would appear safe to operate within 2

hours of cessation of the streptokinase if lysis is unsuccessful or if ischemia progresses. There are a number of contraindications to streptokinase therapy. They are: surgery within the past 10 days (including invasive biopsy, thoracentesis and paracentesis); an intra-arterial diagnostic procedure within the past 10 days (excluding uncomplicated arterial blood-gas measurement employing a 22-gauge or smaller needle); active gastrointestinal bleeding and conditions in which there is a high potential for bleeding (e.g., ulcerative colitis or diverticulitis); defective hemostasis (including coagulation-factor deficiency or thrombocytopenia); a recent (within 2 months) stroke or a condition involving potential central-nervous-system embolism (e.g., mitral-valve disease with atrial fibrillation or subacute bacterial endocarditis); recent trauma with possible internal injuries or external cardiac massage; intracranial neoplasms; severe hypertension (diastolic pressure more than 125 mm Hg); active and progressive cavitating lung disease; acute or chronic hepatic or renal insufficiency; ulcerative cutaneous or mucous-membrane lesions; a history of severe allergic reaction to the thrombolytic agent.[10]

Low-dose local infusion is associated with a low frequency of hemorrhagic complications. Nevertheless patients must be monitored in an intensive care unit and clotting parameters assessed, particularly thrombin, prothrombin and partial thromboplastin times. In spite of close monitoring, hemorrhage occurred in five of our patients. Two were treated within 6 days of surgery with resulting formation of wound hematomas that forced us to withdraw treatment. We do not recommend use of this therapy earlier than 1 month after major surgery. Two patients bled severely from their initial arteriography puncture site. For this reason we recommend that if one contemplates streptokinase therapy, the initial puncture site should be planned with the introduction of the infusion catheter in mind.

Systemic complications such as fever or anaphylaxis were not a problem in this group of patients.

We have observed the development of clot around the catheter, due to stasis in the arterial segment being infused and because of this the catheter must sometimes be repositioned. The tip of the infusion catheter should be placed in the clot initially and may be advanced as lysis occurs to maintain a high dose at the site of the thrombus. Fragmentation of the clot with distal embolization has been observed and could account for worsening of the ischemia in one patient.

It should be emphasized that all patients who had successful clot lysis were placed on intravenous heparin therapy 4 hours after cessation of the streptokinase infusion. Patients who do not have surgically correctable lesions are placed on oral anticoagulation before discharge from hospital.

Streptokinase can be used with success for the lysis of clot in acute arterial occlusion when surgery may be contraindicated because of systemic or local factors. Patients being treated should be closely monitored in an intensive care unit as life-threatening hemorrhage may occur even with local low-dose infusion of streptokinase. Surgically correctable lesions may be demonstrated and appropriately treated after clot lysis.

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Table I—Patients, Anatomic Site, Complications and Results of Intra-Arterial Streptokinase Infusion Therapy

Patient no.	Age, yr	Sex	Site of thrombosis	Duration of symptoms	Duration of infusion, h	Results	Complications	Further reconstruction	Follow-up patency, mo
1	68	F	L FP bypass graft (vein)	10 h	43	Success	None	None	29
2	62	M	L distal SFA-popliteal interposition graft (vein)	3 d	33	Success	None	L distal SFA–popliteal interposition graft (PTFE)	11 (occluded)
3	64	M	R FP bypass graft (vein)	24 h postop	18	Failure	Surgical wound hematoma	Revision R FP graft and thrombectomy	–
4	52	M	L FP graft (vein)	10 d	16	Failure	Severe abdominal retroperitoneal hematoma	Thrombectomy × 2. BK amputation	–
5	71	M	L proximal popliteal artery	3 wk	48	Success	None	None	33
6	67	F	L mid-SFA	2 d	40	Success	Gangrene, L great toe	None	2 till death
7	70	M	L distal SFA	4 d	47	Success (partial)	Minor GI hemorrhage, catheter site hematoma	BK amputation	–
8	64	F	L proximal SFA	6 wk	14	Failure	Surgical wound hematoma	L FP bypass graft (PTFE)	–
9	62	F	L proximal SFA	1 wk	48	Failure	Catheter misplacement	Thromboembolectomy × 2	–
10	80	M	L common iliac artery	4 h	7	Failure	Severe abdominal and retroperitoneal hemorrhage. MI. Death	Distal SFA thrombectomy	–
11	68	M	R popliteal artery stenosis	2 d	48	Success	None	Percutaneous transluminal balloon dilatation	9
12	56	M	R popliteal artery aneurysm	3 d	20	Success	None	R SFA–popliteal bypass graft (vein)	6

FP = femoropopliteal, BK = below-knee, MI = myocardial infarction, GI = gastrointestinal, SFA = superficial femoral artery, PTFE = polytetrafluoroethylene.

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Microvascular Surgery as an Adjunctive Tool in Renal Transplantation

There has been a serious shortage of suitable kidneys for transplantation since this procedure became the treatment of choice for many patients with end-stage renal failure. Some harvested kidneys are discarded due to complicated or injured renal vasculature and some potential living related donors are judged unsuitable because their kidneys have multiple vessels. The authors review the basic microsurgical techniques they have used in such situations to salvage kidneys for transplantation. They emphasize the ex-vivo, "bench", microsurgical method for protecting the kidney from prolonged warm ischemia time (as with multiple complicated in-situ anastomoses). Several illustrative case reports from their recent experience are presented. The authors conclude that microvascular surgery is an important adjunct to the armamentarium of the transplant surgeon.

Depuis que la greffe rénale est devenue le traitement de premier choix de l'insuffisance rénale terminale, on observe une sérieuse pénurie d'organes convenables pour la transplantation. Certains des reins recueillis doivent être rejetés à cause de la complication du réseau vasculaire rénal ou d'une lésion de celui-ci, et certains donneurs potentiels apparentés sont jugés inadéquats parce que leurs reins possèdent de multiples vaisseaux. Les auteurs passent en revue les techniques de microchirurgie qu'ils ont utilisées dans de telles circonstances afin de récupérer des reins pour la greffe. Ils soulignent l'utilité de la méthode de microchirurgie ex-vivo sur "banc d'essai" pour protéger le rein d'une période d'ischémie (comme il en survient dans les cas d'anastomoses in situ compliquées). Ils décrivent plusieurs cas tirés de leur expérience personnelle récente pour illustrer le cas. Les auteurs concluent que la chirurgie microvasculaire est un complément important de l'arsenal thérapeutique du chirurgien spécialiste de la greffe.

Renal transplantation is now the treatment of choice in the majority of patients with end-stage renal disease. Although approximately 60 people in every million annually in North America suffer renal failure and require definitive replacement therapy, the number of kidneys harvested annually is only about 23 per million people. This means that only one-third of those requiring a cadaver kidney are likely to receive one. Within this group of harvested kidneys, about 10% are discarded for various reasons, some with multiple vessels. A number of living related donors are also considered unsuitable because of multiple vessels. In view of the economic advantage and improvement in health of the recipient, an attempt should be made to salvage kidneys with reparable vascular damage (incurred primarily during harvesting) and those with anatomic vascular variations.[1] With microsurgery, such organ salvage procedures can be safely and reliably performed.[2–4] We review the surgical techniques applicable to various vascular arrangements and present illustrative examples from our recent experience.

Surgical Equipment

Standard microsurgical instruments and monofilament nonabsorbable sutures (Ethilon, Prolene, Surgilene) of 7-0, 8-0, 9-0 and 10-0, are used, depending on the diameter of the lumen and thickness of the vessel wall. An operating microscope providing 10 × magnification is used to anastomose finer vessels (2 mm diameter or less) and opthalmologic loupes yielding 3.5 × magnification for larger vessels. Ex-vivo, "bench", microvascular surgery is performed with the kidney cooled in a basin of iced saline.

Multiple Renal Arteries

Over 20% of patients have multiple renal arteries unilaterally and approximately 10% bilaterally. For cadaveric donors, a Carrel aortic patch containing the origins of all renal arteries and anastomosed end-to-side to the recipient external iliac artery is preferred. However, an aortic patch should not be taken from a living donor. Occasionally, the origins of the cadaver donor renal arteries are far apart and would necessitate a large Carrel patch and a very long anastomosis; in such instances the arteries are best taken separately from the donors and microvascular arterioplasty performed ex vivo before transplantation. Following are examples, with illustrative case reports, of the common vascular arrangements.

Arteries of Comparable Calibre

The preferred method for anastomosing two arteries of approximately equal size is the side-to-side technique to create a common opening and a single arterial anastomosis to the recipient. The side-to-side anastomosis is done with a double-armed 7-0 vascular suture running up both cut edges of the vessels (Fig. 1), with reinforcing sutures at the apex and near the end of the new single-vessel opening. This procedure is done in the

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cold basin, thus warm ischemic time is minimized with the single anastomosis required for revascularization. The common opening is also hemodynamically preferrable to two separate smaller openings.

Case 1.—A 38-year-old woman underwent nephrectomy donation for her 35-year-old brother who had rejected two cadaveric renal grafts. A renal arteriogram of the donor revealed double right renal arteries and a single left artery with early branching (0.5 cm) (Fig. 2). To minimize the risk to the donor, the left arterial branches were ligated distal to the branching. The two vessels were then anastomosed ex vivo to create a single opening before revascularization end to side to the recipient external iliac artery. The rewarm ischemic time (venous and arterial anastomosis) was 30 minutes. Both donor and recipient did well. The recipient's serum creatinine value 2 months postoperatively was 100 μmol/L.

Arteries of Unequal Calibre

Although some surgeons[5,6] maintain that small upper pole branches may be ligated, we believe that these small branches should be revascularized whenever possible to avoid potential segmental renal infarction, urinary fistula, postoperative hypertension and graft rupture. A lower pole branch should definitely be revascularized to protect the ureteral blood supply.

The preferred method is end-to-side implantation of the smaller polar artery, which is first spatulated into the main artery (Fig. 3). Interrupted 8-0, 9-0 or 10-0 monofilament sutures are used, depending on the size of the polar branch. A small plastic cannula (e.g., 24-gauge Angiocath) passed through the opening of the main artery into the anastomotic site may prevent injury to the back wall of the side branch during anastomosis. The single renal artery is anastomosed as with a standard transplant.

Case 2.—A 62-year-old man received a cadaveric kidney harvested at another hospital. The donor became hypotensive during the multiorgan harvest (heart, kidneys and liver) and in the hurried dissection, the anatomy was not well appreciated. The left kidney had three arteries, two of comparable size and a third smaller mid-pole vessel (Fig. 4). The smaller artery was ligated and the two larger ones were divided separately. A branch of the upper pole artery was partially caught in a ligature. The ligature was released and the vessel was reanastomosed end-to-side to the upper pole artery with 10-0 sutures. The mid-pole vessel was trimmed and anastomosed likewise to the upper pole artery with interrupted 9-0 sutures (Fig. 4). The two arteries of comparable size were joined side-to-side, creating a single opening. A single anastomosis, end-to-end, to the recipient hypogastric artery was performed. Anastomosis rewarm time was 28 minutes with excellent kidney perfusion. The patient did well and 3 months after transplantation had a serum creatinine level of 160 μmol/L.

Alternative methods of dealing with multiple renal arteries include using the recipient inferior epigastric artery[5] for a separate lower-pole arterial anastomosis and branches of the recipient's hypogastric artery for branch anastomoses.[2,3] This branched autogenous vascular graft method has been found useful by some surgeons.[2,3] Atherosclerotic disease of the recipient artery would render the method less attractive, although endarterectomy has been advocated.[4]

In addition, several in-situ revascularization techniques have been used for kidneys with multiple arteries.[6] These include: multiple separate in-situ arterial anastomoses end-to-side to the external iliac artery; one branch end-to-side to the external iliac artery and one branch end-to-end to the hypogastric artery; and separate anastomoses to branches of the hypogastric artery. The main disadvantage of these methods is that the rewarm ischemic time is prolonged. This is crucial in cases in which cyclosporine is used as the immunosuppressive agent as it has been found that prolonged warm ischemic time (greater than 45 minutes) compounds the nephrotoxic effect of cyclosporine.[7] Multiple in-situ vascular anastomoses are also cumbersome and the likelihood of technical error is increased.

Multiple Renal Veins

Smaller venous branches can safely be ligated. However, double veins of equal size should be anastomosed as with two arteries of equal calibre to avoid venous outflow obstruction.

Case 3.—A 43-year-old woman received a cadaveric kidney with two equal-sized arteries widely spaced along the aorta and with two equal-sized veins. A common caval patch with the two veins was not used as it would have been too wide. A single ostium was created from the two arteries with 8-0 Prolene. The two veins were then anastomosed side-to-side in a similar fashion, using a double-armed 7-0 Surgilene suture. The warm ischemic reanastomosis time with the resultant single artery and single vein was 32 minutes. The nadir of serum creatinine was 190 μmol/L, but the recipient had multiple rejection episodes. His condition stabilized with a serum creatinine value of 270 μmol/L 1 month postoperatively.

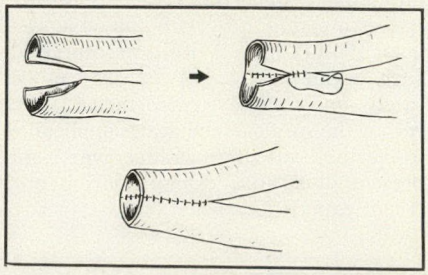

FIG. 1—Side-to-side anastomosis of two vessels of comparable calibre to create single ostium.

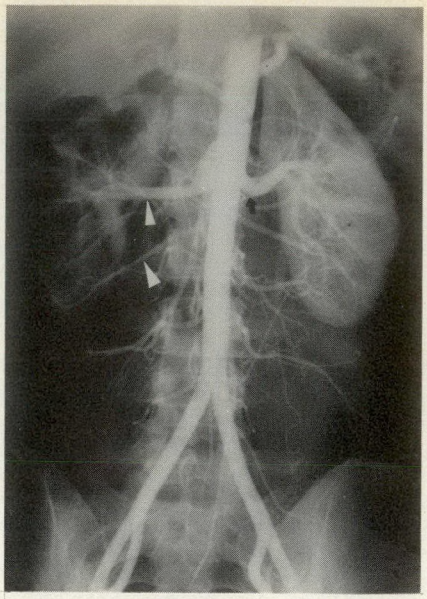

Fig. 2a

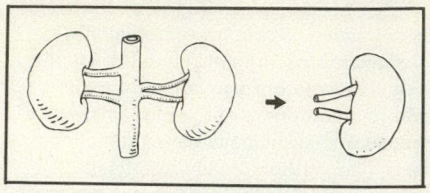

Fig. 2b

FIG. 2—(a) Renal arteriogram of live donor showing double right renal arteries (white arrows) and single left renal artery with very early branching (black arrow). (b) Schematic drawing of left donor nephrectomy. Two arterial branches were taken separately and reconstructed ex vivo.

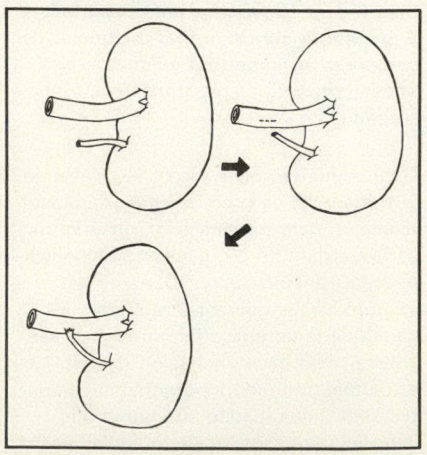

FIG. 3—End-to-side anastomosis of two vessels of unequal calibre.

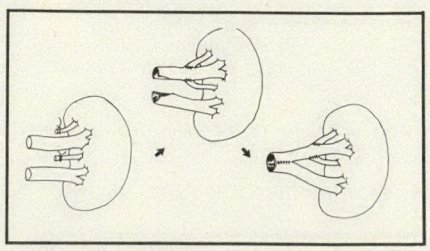

FIG. 4—Schematic drawing of harvested left kidney and its microsurgical reconstruction.

Vascular Injury During Harvesting

When an unsuspected polar vessel or a small, early branch is severed, the techniques mentioned for dealing with multiple vessels are applicable. An additional problem may be loss of vessel length as a result of the injury.

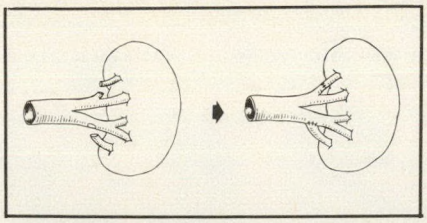

Fig. 5a

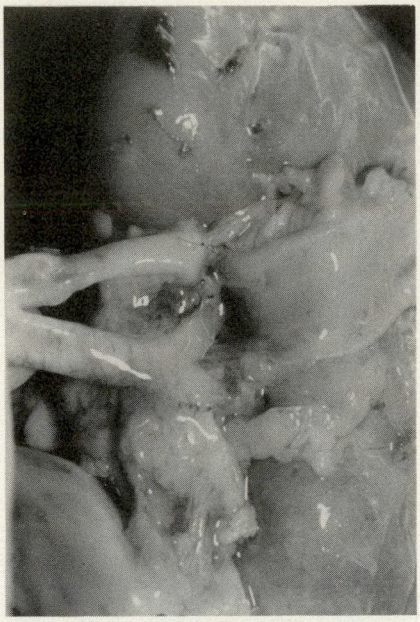

Fig. 5b

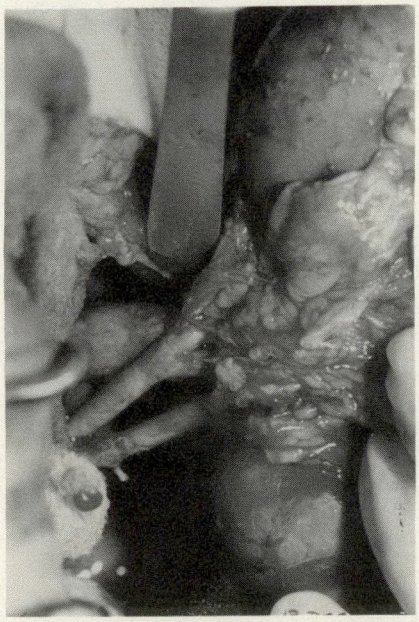

Fig. 5c

FIG. 5—(a) Repair of kidney with severed upper pole branch and area of "non-clearing". Lower pole branch was damaged by ligature. (b) Arterial anastomoses before revascularization. (c) Kidney in patient with patent anastomoses.

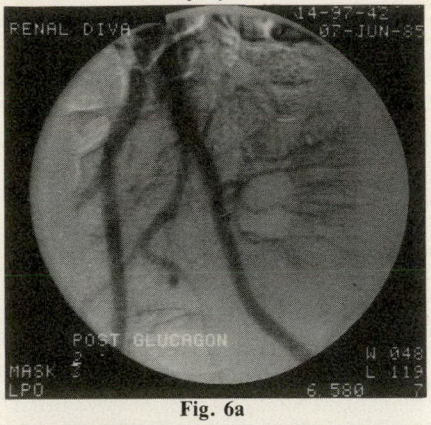

Fig. 6a

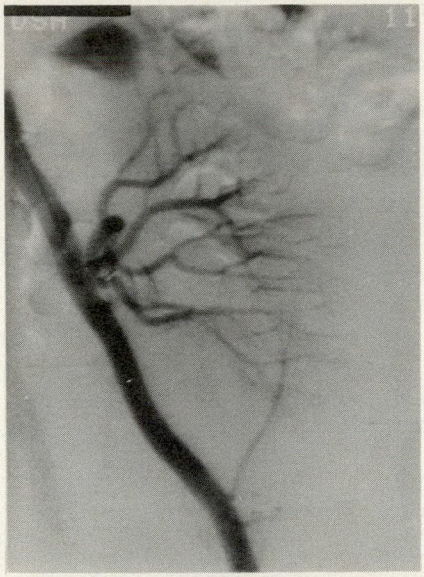

Fig. 6b

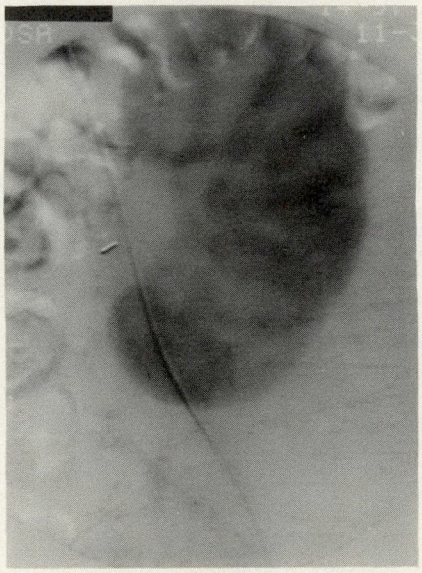

Fig. 6c

FIG. 6—(a) Digital intravenous angiogram of transplanted kidney showing normal vasculature after microvascular reconstruction. Subtraction angiogram of same kidney showing (b) arterial and (c) capillary phase.

Severed Side Branches Without Loss of Length

Both ends of the severed vessels should be examined carefully and trimmed. They are reanastomosed using interrupted 9-0 or 10-0 sutures, preferably with the aid of the operating microscope. Often an area of "non-clearing" is evident on the renal surface where the initial flushing with preservation fluid does not reach the segment supplied by the severed branch. Efforts should be made to flush out the small branch either before or after microsurgical repair.

Severed Side Branch or Polar Vessel With Loss of Length

If length of a vessel is lost or a portion damaged by ligatures and the side branch does not reach its original ostium, the small vessel can often be reimplanted end-to-side to the main renal artery at a site closer to the renal hilum.

The following case demonstrates situations in which side branches are severed with and without loss of vessel length.

Case 4.—A 55-year-old diabetic man received a cadaveric kidney from a 39-year-old donor, harvested elsewhere. At the time of harvesting, a lower-pole branch with early take-off was severed. The distal end was damaged by a ligature. At the time of flushing, an area 2 × 2 cm in the upper pole did not clear (Fig. 5). On closer examination, a small upper pole branch obscured by perinephric fat had been sharply transected. There was no loss of vessel length from this upper pole branch. The lower pole branch with some loss of length was reimplanted into the side wall of the main artery with 8-0 interrupted Ethilon sutures at a site closer to the renal hilium. The upper pole branch was reanastomosed end-to-end with interrupted 10-0 Ethilon sutures. The main renal artery was then flushed in the cold basin to ensure watertight anastomoses and to flush out the "non-cleared" area in the upper pole. Surgical anastomosis rewarm ischemic time was 38 minutes. The recipient had acute tubular necrosis, lasting 3 weeks, before the kidney started functioning but did well. His serum creatinine value 5 months after operation was 150 μmol/L.

In cases in which loss of length from the severed vessel precludes direct anastomosis to the main renal artery, interposition of a vascular graft (preferably autogenous) or use of the inferior epigastric artery may be feasible.[5]

Clinical Outcome

We have used microsurgical angioplasty techniques to handle kidneys with multiple vessels. In the past 8 months, 11 such repairs on transplant kidneys were performed. The average ex-vivo operating time was 45 minutes. Kidneys that required extensive microvascular reconstruction were repaired ex vivo before the recipient was anesthetized. Repairs that

were less complex (e.g., side-to-side anastomosis of double arteries) were performed just before vascular anastomosis of the recipient vessels.

We did not routinely perform arteriography to assess the microvascular repair, because of the inherent risks. Radioactive nuclear scans of all transplanted kidneys have demonstrated prompt perfusion with no segmental filling defects. Digital intravenous angiography and standard arteriography on selected patients demonstrated normal vasculature (Fig. 6). There was no case of hemorrhage, calyceal fistula formation or immediate postoperative hypertension.

Discussion

Discarding a donor organ is a waste of precious material and discouraging to donor hospitals. Efforts to reduce this wastage must be pursued. In the past, organs may have been discarded because of multiple arteries or vascular injury. We believe the majority of kidneys can be salvaged by applying the basic microsurgical techniques outlined. Moreover, multiple renal vessels requiring multiple (and often cumbersome) in-situ anastomoses can be modified structurally to facilitate the revascularization procedure. The ex-vivo microvascular techniques are not complex and do not require elaborate surgical equipment. A combination of the basic anastomotic techniques is often required to deal with various vascular arrangements. This portion of the surgery can be performed ex vivo in the cold basin before the recipient is anesthetized, so that patient anesthetic time is not prolonged. More importantly, the vascular anastomoses to recipient vessels are much simpler. The warm ischemic time is shortened, compared with the time required for multiple in-situ anastomoses, which is of paramount importance in patients receiving a nephrotoxin like cyclosporine. The Canadian Multicentre Transplant Study Group[7] observed that the cyclosporine nephrotoxicity effect is exacerbated by a warm ischemic time exceeding 45 minutes.

In summary, we have outlined the various clinical situations in which microsurgical repair can be used to salvage some kidneys for transplantation and to facilitate revascularization in other kidneys. We conclude that microvascular surgery is an important adjunct to the armamentarium of the transplant surgeon.

We thank Ms. N. Somerville, Division of Nephrology, University Hospital, for her expert, artistic illustrations.

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Therapeutic Classification
Antibacterial agent
Indications
The following infections when caused by susceptible microorganisms:
- upper and lower respiratory tract (particularly chronic bronchitis and including acute and chronic otitis media)
- urinary tract: acute, recurrent and chronic
- genital tract: uncomplicated gonococcal urethritis
- gastrointestinal tract
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'Bactrim' for Infusion is indicated in serious systemic infections (e.g. meningitis, septicemia) caused by susceptible organisms and in *Pneumocystis carinii pneumonitis*, when oral administration is impractical.
Not indicated in infections due to *Pseudomonas*, *Mycoplasma* or viruses.
Contraindications
Known hypersensitivity to trimethoprim or sulfonamides; marked renal impairment where serum determinations cannot be performed; marked liver damage; blood dyscrasias.
During pregnancy or lactation, and in infants under two months old.
Warnings
Fatalities have occurred rarely with sulfonamides due to severe reactions, e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.
Precautions
Appraise benefit against risk in patients with liver damage, renal damage, urinary obstruction, blood dyscrasias, allergies, or bronchial asthma. Beware of kernicterus in neonates. Reduce dosage and determine serum concentrations in patients with renal impairment. Do not use if creatinine clearance is below 15 mL/min. Monitor blood counts during long-term therapy and in patients disposed to folate deficiency, including those on anticonvulsant therapy. Folinic acid may reverse signs of folate deficiency.
Consider possible superinfection with a non-sensitive organism.
Drug Interactions: Antagonists: PABA and its derivatives. Potentiators: urinary acidifiers, oral anticoagulants, sulfonylurea hypoglycemics, phenylbutazone, oxyphenbutazone, indomethacin, sulfinpyrazone and salicylates.
Adverse Reactions
Hematological: primarily, neutropenia and thrombocytopenia; less frequently, leukopenia, aplastic or hemolytic anemia, purpura, agranulocytosis, and bone marrow depression. Occur particularly in the elderly and are mostly asymptomatic and reversible on withdrawal.
Most frequent: nausea, vomiting, gastric intolerance, rash.
Less frequent: diarrhea, constipation, flatulence, anorexia, pyrosis, gastritis, gastroenteritis, urticaria, headache, and elevated alkaline phosphatase and serum transaminase.
Occasional: erythema, edema, pruritis, toxicoderma, photosensitivity, glossitis, stomatitis, dyspepsia, dry mouth, dysuria, oliguria, anuria, hematuria, urgency, dyspnea, tremour, vertigo, tiredness, jaundice, vision troubles, drug fever, alopecia, epistaxis, black tongue, elevated BUN, NPN, serum creatinine or urinary protein and anaphylactoid reactions.
Rare: goiter, diuresis and hypoglycemia have occurred with sulfonamides.
Dosage and Administration
INTRAVENOUS
Parenteral therapy is indicated if patient cannot take oral medication or if high serum concentrations are required rapidly.
PARENTERAL TREATMENT SHOULD BE TERMINATED AND ORAL TREATMENT INSTITUTED AS SOON AS POSSIBLE. CAUTION – 'BACTRIM' FOR INFUSION MUST BE DILUTED IN STERILE D5W, RINGER'S OR NaCl 0.9% SOLUTION PRIOR TO ADMINISTRATION. DIRECT INTRAVENOUS INJECTION NOT RECOMMENDED. DO NOT MIX WITH OTHER DRUGS OR SOLUTIONS. For method of dilution and infusion administration, see Package Insert.
Pneumocystis carinii pneumonitis:
Children and adults: 5 mg trimethoprim/kg + 20 mg sulfamethoxazole/kg q.i.d. until oral therapy can be instituted.
Serious systemic infections:
Adults: 160 to 240 mg trimethoprim + 800 to 1200 mg sulfamethoxazole (10-15 ml 'Bactrim' for Infusion) every 6, 8 or 12 hours, depending on severity of infection.
Children: 5 to 10 mg trimethoprim/kg/day + 25 to 50 mg sulfamethoxazole/kg/day in 2-4 equally divided doses.
PATIENTS WITH IMPAIRED RENAL FUNCTION
Not recommended if creatinine clearance (Cl_{cr}) less than 15 ml/min. At Cl_{cr} 15-30 ml/min: 1/2 usual regimen. At Cl_{cr} above 30 ml/min: usual regimen.
Supply
Adult tablets: 80 mg trimethoprim and 400 mg sulfamethoxazole. Bottles of 100 and 500. Unit dose: boxes of 100. DS tablets: 160 mg trimethoprim and 800 mg sulfamethoxazole. Bottles of 100 and 250. Pediatric tablets: 20 mg trimethoprim and 100 mg sulfamethoxazole. Bottles of 100. Suspension: Cherry-flavoured, 40 mg trimethoprim and 200 mg sulfamethoxazole, per 5 ml. Bottles of 20, 100 and 400 ml. Solution for Infusion: Each ml contains 80 mg sulfamethoxazole and 16 mg trimethoprim, for infusion with D5W, Ringer's or NaCl 0.9% solution. Packs of 10 x 5 ml vials, single 30 ml vials and 10 x 5 ml ampoules.
Product Monograph available on request.
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Original Research in medicine and chemistry

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Les complications du traitement du cancer du col utérin par radiothérapie

Le traitement du cancer du col utérin par radiothérapie a conduit à des complications soit digestives, urologiques ou gynécologiques chez 275 des 939 malades (29.3%) traitées à l'hôpital Notre-Dame de Montréal, de 1979 à 1981.

Dans 55 cas (5.9%), il a fallu recourir à un traitement chirugical pour pallier à 73 complications: 42 complications digestives sous forme d'occlusions (25), de fistules (13) et de perforations (4); 22 complications urologiques sous forme d'occlusions (16), de fistules (5) et d'hémorragie (1); 6 complications gynécologiques, sous forme d'hémorrhagie (3) ou de nécrose utérine (3); 1 nécrose cutanée, 1 vasculaire et 1 osseuse.

Les auteurs n'ont pas trouvé de corrélation directe entre l'incidence des complications et certains facteurs favorisants tel que le type de radiothérapie administrée, l'âge des malades traités, le stade de la néoplasie et la présence de chirurgie gynécologique antérieure au traitement radiothérapeutique. Par contre, la relation entre l'incidence des complications et la dose de rayons administrée et la présence de chirurgie gynécologique postérieure au traitement radiothérapeutique est hautement significative.

Dans le groupe des complications traitées par la chirurgie, la morbidité a été élevée: les 55 malades ont dû subir en moyenne 2.36 interventions, 2.98 anesthésies générales, 1.81 hospitalisations d'une durée moyenne de 75.7 jours et 21 patientes sont devenues porteuses d'une ou plusieurs stomies définitives. La mortalité a été de 5.45%.

Le traitement chirurgical a été individualisé pour chaque cas. Les complications digestives et urologiques ont été traitées par une dérivation lorsqu'une résection aurait été trop extensive ou dangereuse. Des résections limitées ont été utilisées pour traiter aussi bien les occlusions et les fistules que les perforations chaque fois que cela était possible. La majorité des lésions du rectum ont été traitées par opération de Hartmann et colostomie.

Of 939 patients treated by radiotherapy for carcinoma of the cervix at the hôpital Notre-Dame in Montreal, between 1979 and 1981, 275 (29.3%) had digestive, urologic, gynecologic, vascular, osseous and cutaneous complications. Surgery was necessary to treat 73 complications in 55 patients (5.9%): 42 digestive (25 occlusions, 13 fistulas and 4 perforations); 22 urologic (16 occlusions, 5 fistulas, 1 hemorrhage); 6 gynecologic (3 hemorrhage and 3 uterine necrosis); 1 cutaneous, 1 vascular and 1 osseous necrosis.

No direct correlation was found between the incidence of the complications and certain predisposing factors such as the type of radiotherapy, patients' age, stage of the disease and gynecologic surgery before radiotherapy. However, there was a strong correlation between the incidence of complications and the dose of radiotherapy and the need for gynecologic surgery after radiotherapy.

High morbidity was observed in the 55 patients treated surgically: they had to undergo a mean of 2.36 operations each, 2.98 general anesthetics, 1.81 hospitalizations (mean duration 75.7 days); 21 had one or more definitive stomas. The death rate was 5.45%.

Surgical treatment was individualized. Limited resections were performed for occlusions, fistulas and perforations whenever it was technically feasible to treat digestive and urologic complications.

A bypass procedure was used when resection would have been too extensive or dangerous. The majority of rectal lesions were treated by colostomy and a Hartmann procedure.

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La radiothérapie est un mode thérapeutique accepté dans le traitement du cancer invasif du col utérin. La survie globale à 5 ans qui était d'environ 35% dans les années 40, est actuellement de 65%.[1] Dans notre centre, une étude récente a montré que la survie à 5 ans a atteint 78.6% et celle à 10 ans, 74.3% pour les néoplasies du col au stade Ib (FIGO) traitées par cette modalité.[2]

Cette thérapeutique est cependant grevée de complications dont l'éventail est très large.[3–18] Dans la majorité des cas, un traitement médical suffit à enrayer les complications d'iléite, de rectite et de cystite mais chez un nombre non négligeable de malades, la gravité des complications impose une approche chirurgicale.[6,17,18–32]

La présente étude porte la nature et l'étendue du traitement des complications post-radiothérapie en fonction de la dose administrée, du type de radiothérapie reçue, de l'âge des malades traitées, du stade de la néoplasie, de la durée des examens de surveillance et de la présence ou de l'absence de chirurgie antérieure ou postérieure à l'irradiation. On s'est attaché plus particulièrement à étudier la morbidité et la mortalité ainsi que le résultat du traitement des complications post-radiothérapie ayant nécessité une correction chirurgicale.

Matériel et méthodes

De janvier 1969 à décembre 1981, 1086 malades porteuses d'un cancer invasif du col utérin ont été traitées par radiothérapie à l'hôpital Notre-Dame.

Les dossiers médicaux de ces patientes ont été étudiés. Cent quarante-sept n'ont pas été retenus pour les raisons suivantes: abandon prématuré du traitement, absence d'examens de post-cure ou radiothérapie à titre palliatif pour une maladie à un stade trop avancé. Ce qui porte le nombre total de dossiers utilisés à 939.

La période de surveillance varie d'un à 14 ans. Cinq cent cinq malades ont été suivies d'un à 5 ans, 294 de 5 à 10 ans et 140 pendant plus de 10 ans après leur traitement.

Les techniques d'irradiation ont varié suivant le stade clinique de la maladie. Cependant, les doses à la tumeur se situèrent entre 5000 rad en 5 semaines et 7500 rad en 7 semaines, avec des extrêmes de 3600 à 13 200 rad. Ainsi, 9.9% des malades ont reçu moins de 5000 rad, 39.5% ont reçu entre 5000 et 8000 rad, 41.3% entre 8000 et 10 000 rad et 9.3% 10 000 rad et plus (tableau I).

En général, le traitement consista dans l'irradiation du bassin, des trous obturateurs aux crêtes iliaques, par un champ de 225 cm^2 suivie d'une surdose à la tumeur de 2000 rad par irradiations endocavitaires (sonde endo-utérine plus colpostat ou moulage vaginal radifère) (727 cas). Cependant, 166 patientes n'eurent qu'une irradiation externe et 46 malades eurent une irradiation endocavitaire isolée.

Tous les plans de traitement furent faits avec des courbes d'isodose calculées au moyen d'un ordinateur.

Répartition des stades cliniques

Trois cent quarante-trois malades furent traitées pour cancer au stade I (36.5%), 290 pour un stade II (30.9%), 187 pour un stade III (19.9%) et 42 pour un stade IV (4.5%). Enfin, 77 patientes (8.2%) n'ont pu être classifiées, le diagnostic de cancer du col ayant été effectué chez elles sur un échantillon anatomopathologique après hystérectomie pour raisons diverses.

Distribution de l'âge

La moyenne d'âge des patientes traitées fut de 54.8 ans avec un écart de 18 à 85 ans. Au moment du traitement, 26.6% des malades avaient moins de 45 ans, 36.9% avaient entre 45 et 60 ans et 36.5% avaient 60 ans et plus.

Classification des complications post-radiothérapie

Nous avons classifié les complications survenues après la radiothérapie suivant une modification du système de classification proposé par Kagan et collaborateurs[33] (M = réactions aiguës aux radiations ou complications chroniques requérant un traitement médical; CH = complications requérant un traitement chirurgical): la classe 0 à MI représente l'absence ou la présence de réactions aiguës temporaires réversibles survenant pendant le traitement de radiothérapie et se résolvant dans les semaines qui suivent l'arrêt de celui-ci. Elles se présentent sous forme de douleurs abdominales, diarrhées, cystites, rectites et dyspareunies.

La classe MII représente les complications tardives survenant de quelques mois à plusieurs années après la radiothérapie et évoluant de façon chronique sous forme de subocclusion, diarrhées, cystites, rectites, épisodes d'hémorragie digestive basses et fistules mineures répondant en général de façon satisfaisante à un traitement médical.

La classe CH représente les mêmes complications que la classe précédente mais s'exacerbant ou se compliquant et nécessitant une approche chirurgicale pour leur traitement.

Traitement chirurgical antérieur ou postérieur à la radiothérapie

Cent quatre-vingt-deux malades avaient subi des interventions chirurgicales gynécologiques majeures soit antérieurement (134), postérieurement (44) ou encore antérieurement et postérieurement (4) à la radiothérapie.

Chez les patientes opérées avant la radiothérapie, on dénombre 26 hystérectomies subtotales, 83 hystérectomies totales et 25 hystérectomies radicales.

Après le traitement radiothérapeutique, 11 malades ont subi une hystérectomie totale, 20 une hystérectomie radicale et 13 patientes ont subi une exentération pelvienne soit pour compléter le traitement radiothérapeutique, soit pour traiter les récidives.

Enfin, quatre malades ont subi une hystérectomie antérieurement à la radiothérapie et celle-ci fut suivie d'une exentération pelvienne.

De plus, 31 patientes ont eu des interventions chirurgicales mineures longtemps avant le traitement de la néoplasie utérine telles que cure de hernie inguinale, appendicectomie, ovariectomie, et résection de diverticule de Meckel. Ce dernier groupe ne fait pas l'objet d'une étude statistique particulière dans les relations entre le traitement chirurgicale antérieur ou postérieur à la radiothérapie et les complications.

Analyse statistique

La statistique du χ^2 a été utilisée pour vérifier l'indépendance de certaines variables.

Les résultats ont par ailleurs fait l'objet d'une analyse de régression multiple, l'objectif de cette méthode statistique étant de prédire l'apparition de l'une ou l'autre complication (variable — cible) à partir de plusieurs facteurs (variable — prédictrice) considérés simultanément.

Résultats

Incidence, morbidité, mortalité et traitement des complications

Classe 0–MI.—Dans cette catégorie de complications, on dénombre 664 malades (70.7%) (tableau II). Elles ont été traitées avec succès par des moyens conservateurs: mesures hygiéniques et diététiques telles que régime pauvre en résidus, analgésiques, antispasmodiques, émollients, lavements aux stéroides et repos.

La morbidité a été négligeable et la mortalité a été nulle.

Classe MII.—On y compte 220 malades (23.4%) (tableau II). Ces complications évoluant de façon chronique ont en général répondu de façon satisfaisante au traitement médical tel que décrit dans la classe 0–MI mais dans un certain nombre de cas, elles ont évolué vers la classe suivante (CH).

Dans cette classe, le taux de réhospitalisation pour traitement ou investigation a été de 14% et la mortalité a été nulle.

Classe CH.—Chez 55 malades (5.9%), il a fallu recourir à un traitement chirurgical pour pallier à 73 complications post-radiothérapeutiques (tableau II).

Le délai d'apparition des complications a varié d'un mois à 13 ans (moyenne: 2 ans et 8 mois).

On relève 42 complications digestives dont 25 occlusions de l'intestin grêle ou du côlon, 13 fistules entéro-vaginales ou entéro-cutanées et 4 perforations intestinales.

On compte 22 complications urologiques sous forme d'occlusions urétérales,

Tableau I—Dose d'irradiation à la tumeur chez 939 patientes

Dose, rad × 10^3	No. (%) de patientes
< 5	93 (9.9)
5 – 6	64 (6.8)
6 – 7	124 (13.2)
7 – 8	183 (19.5)
8 – 9	244 (26.0)
9 – 10	144 (15.3)
10 – 11	56 (6.0)
≥ 11	31 (3.3)

Tableau II—Incidence des complications

Classe	No. (%) de patientes
0–MI	664 (70.7)
MII	220 (23.4)
CH	55 (5.9)

0–MI = réaction secondaire à la radiothérapie aiguë et réversible, MII = complication tardive et chronique nécessitant un traitement médical soutenu, CH = complication nécessitant un traitement chirurgical.

de fistules urinaires hautes ou basses et d'hémorragie.

Enfin, il y eut six complications gynécologiques dont trois hémorragies intarissables et trois nécroses massives de l'utérus, une complication cutanée sous forme de nécrose étendue de la région sacrée, une complication vasculaire sous forme de fibrose rétro-péritonéale ayant entrainé un syndrome de Leriche, et une complication osseuse sous la forme de fracture pathologique des deux cols du fémur.

Les occlusions digestives ont été traitées par 6 viscérolyses, 4 dérivations iléo-coliques, 7 résections sementaires du grêle, 16 résections coliques segmentaires ou hémicolectomies et 1 amputation du rectum. Elles ont conduit à six colostomies définitives et six colostomies temporaires.

Les fistules digestives ont nécessité trois opérations de Hartmann, cinq résections coliques et deux résections segmentaires du grêle. Neuf malades dans ce groupe ont eu des colostomies définitives et deux, des colostomies temporaires.

Les perforations digestives ont été traitées par opération de Hartmann chez deux malades, une résection du grêle chez une autre et une caecostomie chez la quatrième. Deux stomies ont été définitives et une temporaire.

Vingt-deux complications urologiques sont survenues chez 15 malades; soit 16 sténoses urétérales, 2 fistules urétéro-vaginales, 2 fistules vésico-vaginales, 1 fistule urétéro-cutanée et 1 cystite hémorragique. Elles ont conduit à 10 urétéro-cysto-néostomies, 6 trans-urétéro-urétéro-stomies, 2 urétérolyses, 2 iléo-urétéro-stomies, 1 cystectomie complète. 1 néphrectomie, 1 urétéro-sigmoidostomie et 1 hémostase vésicale, avec 5 conduits iléaux définitifs.

Quant aux complications gynécologiques, elles ont nécessité trois ligatures des deux artères hypogastriques, deux hystérectomies élargies et une exentération antérieure avec une stomie définitive.

La complication de nécrose cutanée a été traitée par un lambeau de rotation, débridement et nouvelle greffe cutanée. La complication vasculaire a été traitée par un pontage axillo-fémoral droit et fémoro-fémoral. Enfin, une des deux fractures pathologiques du col du fémur a été traitée par prothèse de Moore.

Le traitement de ces complications a nécessité un total de 130 interventions chirurgicales avec pour chaque malade une moyenne de 1.81 ± 0.75 hospitalisations (écart de 1 à 6) d'une durée de 75.7 ± 48.6 jours (9 à 219) et une moyenne 2.98 ± 1.9 anesthésies générales (1 à 10).

La morbidité postopératoire a été importante avec 15 épisodes de septicémie, 5 fistules digestives, 4 éventrations, 5 nécroses de colostomie, 13 infections de plaie, 6 iléus paralytiques, 2 pneumonies, 3 insuffisances rénales graves dont une seule a été réversible, 3 thrombo-phlébites profondes, 1 embolie pulmonaire, 1 infarctus du myocarde, 2 pathologies psychiatriques et 1 atteinte du nerf VIII par toxicité à la gentamicine. Sur les 55 malades traitées, 21 sont devenues porteuses d'une ou plusieurs stomies externes définitives.

Trois patientes sont décédées dans la période postopératoire immédiate.

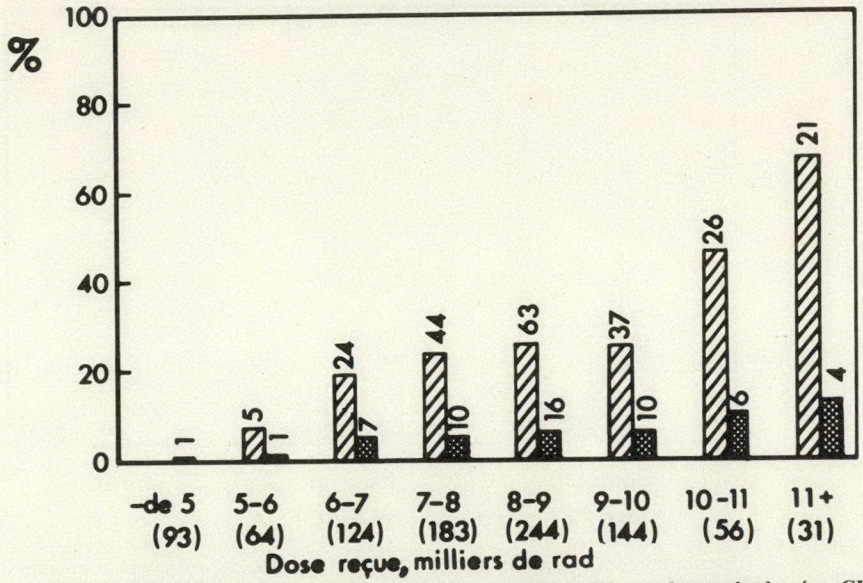

FIG. 1—Distribution des types de complications (classes MII = colonnes hachurées, CH = colonnes pointillées) en fonction de la dose d'irradiation.

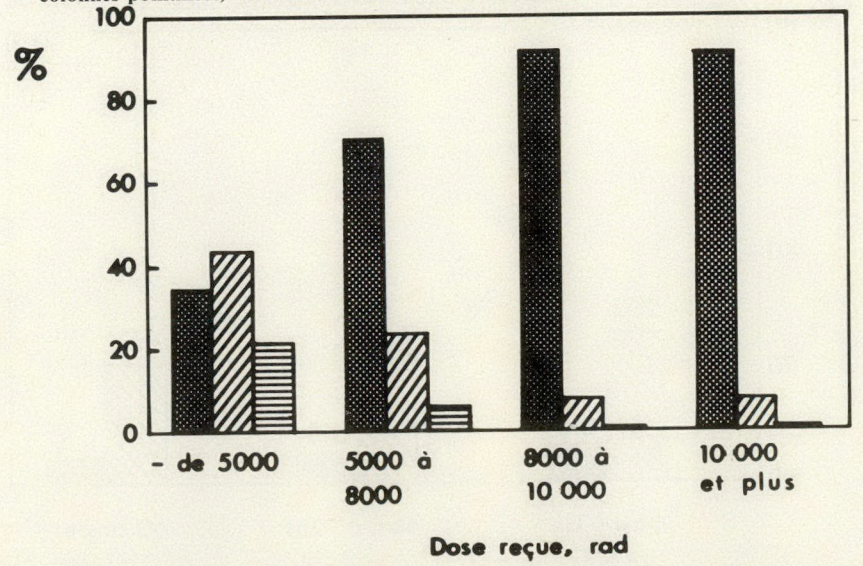

FIG. 2—Relation entre la dose reçue et le type d'irradiation utilisé (combinée = colonnes pointillées, externe = colonnes hachurées, interne = colonnes lignées).

Relation entre la dose d'irradiation et les complications

Il existe une relation très significative entre la dose de rayons administrée, le nombre et la gravité des complications post-radiothérapie ($\chi^2 = 112, 6$, dl = 14, $p < 0.0001$). Comme en témoigne la figure 1, des 93 malades ayant reçu moins de 5000 rad, aucune n'est classifiée MII, et une seule (1.1%) est classifiée CH, tandis que des 31 patientes ayant reçu 11 000 rad ou plus, 67.7% sont classifiées MII et 12.9% CH.

Relation entre le type de radiothérapie administrée et les complications

Bien que le taux de complications MII et CH soit plus élevé lorsque des techniques d'irradiations combinées ont été utilisées, la relation n'est pas statistiquement significative ($p = 0.1191$) (fig. 2).

Cependant, l'analyse statistique fait ressortir que ce sont les patientes qui ont été traitées par radiothérapie externe et interne combinées qui ont reçu le plus d'irradiation ($\chi^2 = 178.3$, dl = 6, $p < 0.0001$) (fig. 3).

Relation entre l'âge des malades traitées et les complications

On ne trouve pas de relation statistiquement significative entre l'âge auquel les malades ont reçu de la radiothérapie et les complications post-radiothérapie (fig. 4). Tout au plus, décèle-t-on une tendance à une dimunition du taux de complications MII et CH avec la progression de l'âge des groupes traités.

Relation entre le stade de la néoplasie traitée et les complications

On note que plus les stades sont précoces, plus leur traitement se solde par des complications de type MII et CH (tableau III). Cependant, la relation n'est pas statistiquement significative ($p = 0.17$).

Relation entre la durée des examens de surveillance et le type de complications

Comme le démontre le tableau IV, les complications de type MII sont passées de 18.4% après 1 à 2 ans de surveillance post-thérapeutique pour se stabiliser aux alentours de 25% par la suite.

Les complications nécessitant une solution chirurgicale sont passées de 2.2% à 10.5% entre la 2e et la 5e année de surveillance pour se stabiliser ensuite aux environs de 5%.

Relation entre la présence ou l'absence de chirurgie antérieure ou postérieure à l'irradiation et l'apparition des complications

Le taux de complications n'est pas grevé par la chirurgie gynécologique subie avant la radiothérapie, quelqu'en soit le type (tableau V).

Le nombre de patientes ayant subi une intervention en période pré- et post-radiothérapie est trop limité (4) pour pouvoir avoir une signification statistique.

Par ailleurs, le taux de complications CH est significativement plus élevé ($p < 0.001$) chez les patientes opérées après le traitement de radiothérapie (tableau VI). Ce sont en particulier les malades qui ont subi des hystérectomies radicales et des exentérations pelviennes qui sont les plus fragiles.

Discussion

Les techniques modernes de radiothérapie permettent une orientation et une concentration optimale de la dose cytotoxique vers et sur la lésion néoplasique visée. Malgré tout, les viscères sains avoisinants sont la plupart du temps atteints à des degrés divers par les rayons utilisés[34] et le degré de gravité de cette atteinte est dose-dépendant et varie également en fonction d'autres facteurs tels que la susceptibilité individuelle, la radiosensibilité spécifique des organes touchés, le type de radiothérapie administrée, l'âge des malades traitées, le stade de leur néoplasie, la présence de chirurgie au niveau de la sphère irradiée antérieurement ou postérieurement à la radiothérapie, l'obésité, la diabète et les maladies inflammatoires du petit bassin.[35]

Des doses optimales ne dépassant pas 5000 rad sont recommandées afin d'éviter les complications.[3,13,19,27,28,36] A ces niveaux, le risque de lésion des viscères se situe entre 1% et 5%, mais il atteint progressivement des taux de 25% à 50% lorsque la dose de rayons utilisée dépasse ce plafond optimal.[34]

Notre série confirme cet état de chose. Elle démontre que la relation entre la dose d'irradiation et le taux de complications est hautement significative ($p < 0.0001$). Au total, sur les 939 malades, les 220 (23.4%) qui ont souffert de complications de type MII, avaient toutes reçu plus de 5000 rad et 55 (5.9%) ont présenté des problèmes de type CH (tableau II). Aux extrêmes, sur les 93 patientes ayant été traitées avec moins de 5000 rad, aucune n'a été classée MII et une seule (1.1%) a été classée CH, alors que dans le groupe des 31 malades traitées avec 11 000 rad et plus, 21 (67.7%) ont souffert de complications MII et 4 (12.9%) ont dû avoir recours à une solution chirurgicale (CH) (fig. 1).

Le délai d'apparition des complications peut être extrêmement long. Dans notre étude, il a été limité à 14 ans par la durée de la surveillance post-thérapeutique,

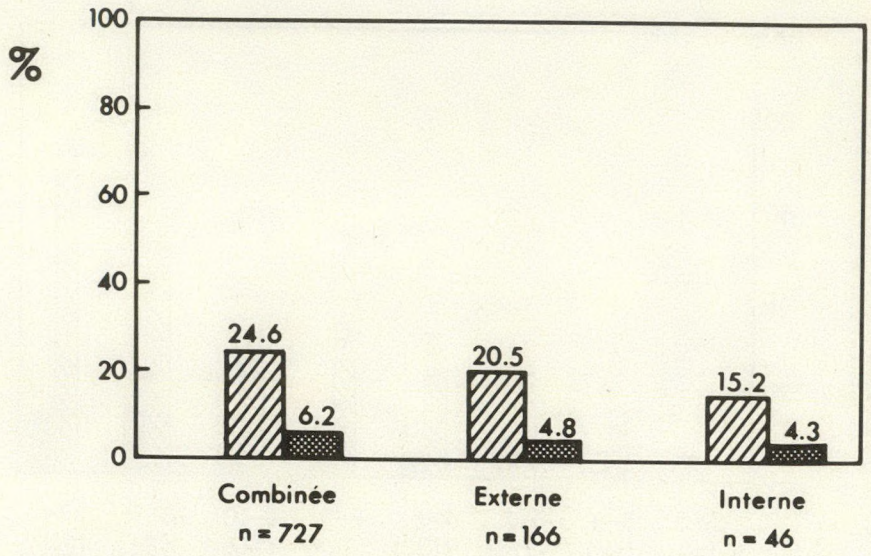

FIG. 3—Distribution des complications selon le type d'irradiation reçue (MII = colonnes hachurées, CH = colonnes pointillées).

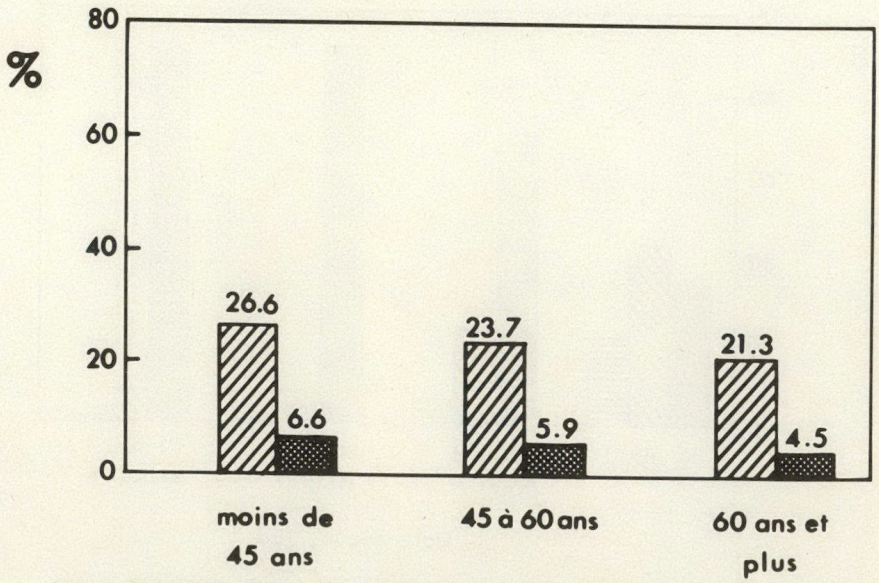

FIG. 4—Distribution des types de complications en fonction de l'âge (MII = colonnes hachurées, CH = colonnes pointillées).

mais il peut atteindre 20 ans et plus.[18,34-37] De plus, l'incidence des complications reste stable dans le temps (plus ou moins 25% pour la classe MII et plus ou moins 5% pour la classe CH).

Ceci attire une fois de plus l'attention sur l'importance des antécédents radiothérapeutiques pour l'évaluation d'un malade présentant un problème abdominal quel que soit le délai écoulé depuis l'irradiation.

Contrairement à d'autres études,[6,16,27,35,38,39] nous n'avons pas trouvé de corrélation directe entre l'incidence des complications MII et CH et certains facteurs favorisants étudiés tels que le type de radiothérapie administrée, l'âge des malades traitées et le stade de la néoplasie. Le seul dénominateur commun statistiquement significatif reste la dose de rayons administrée. L'analyse de régression multiple confirme cet état de chose: l'étude des variables telles que la dose d'irradiation, l'âge, le type de radiothérapie administrée, le stade de la néoplasie et la présence ou l'absence de chirurgie antérieure ou postérieure à l'irradiation révèle que seule la dose d'irradiation est significative (r – multiple = 0.326, $F = 99.8$, $p < 0.0001$). Ainsi, ce sont les malades qui ont subi un traitement de radiothérapie combiné (interne et externe) qui ont reçu le plus de rayons (figs. 2 et 3); les malades jeunes ont un taux plus élevé de complications mais ce sont elles qui ont été traitées le plus agressivement; ainsi, 64.4% des patientes de moins de 45 ans ont reçu plus de 8000 rad contre 58.3% pour les patientes âgées de 45 à 60 ans et 49.7% pour les malades âgées de plus de 60 ans ($p < 0.0008$).

Enfin, la relation entre le taux de complications et les stades traités est également essentiellement dose-dépendante. Les stades précoces ont en général été traités plus vigoureusement que les stades III et IV ce qui explique leur taux de complications légèrement plus élevé (tableau III).

Par ailleurs, bien que 31.3% de nos malades ayant subi une intervention gynécologique antérieure à la radiothérapie aient présenté des complications de type MII et CH, la relation avec le groupe n'ayant jamais subi de chirurgie n'est pas significative (tableau V), contrairement aux résultats d'autres publications.[6,35-37] La relation est par ailleurs hautement significative ($p < 0.001$) en ce qui concerne les complications de type CH lorsque l'on compare le groupe ayant nécessité un traitement chirurgical additionnel à la radiothérapie pour le traitement de leur cancer par rapport au groupe exempt de chirurgie (tableau VI). Ce sont en particulier les malades qui ont subi des hystérectomies radicales et des exentérations pelviennes qui paient le plus lourd tribut. (Notre étude comporte cependant un biais puisque pour des raisons techniques, nous n'avons pu introduire les 31 malades ayant subi des interventions abdominales mineures avant le traitement de leur cancer du col.)

Les réactions secondaires aux radiations de type 0–MI sont aiguës. Elles sont le lot de la majorité des malades traitées par radiothérapie pour cancer du col. Elles sont heureusement bénignes et ne durent que le temps du traitement radiothérapeutique. La morbidité est négligeable et un traitement conservateur minimal suffit à la juguler. Elle est le résultat d'une atteinte des cellules muqueuses radiosensibles du tractus gastro-intestinal et n'a pas de relation avec les complications tardives.[34]

Les complications de type MII sont plus insidieuses et ont d'emblée un caractère de chronicité. Le plus souvent, elles apparaissent dans un délai de 6 mois à 2 ans après le traitement. Dans notre étude, leur fréquence se stabilise aux alentours de 25% après ce délai. Elles correspondent à une vasculite oblitérative, une atrophie muqueuse et une fibrose de la paroi intestinale.[34]

La morbidité de ces complications requiert de fréquentes hospitalisations pour investigation ou traitement. Un traitement conservateur ne réussit pas toujours à stabiliser le processus. La résistance au traitement médical avec rectorragies sévères, ténesme et douleurs rebelles, occlusions digestives et fistules, et détérioration de l'état général conduit une certaine porportion de ces malades vers la classe CH. Cette évolution peut survenir n'importe quand et elle est imprévisible même lorsque le délai écoulé depuis le traitement radiothérapeutique est de plusieurs années. La symptomatologie peut faire penser à une récidive de la néoplasie. Elle impose des examens pelviens sous anesthésie générale, de multiples biopsies, des rectosigmoidoscopies, des pyélographies endoveineuses et des cystoscopies.

Comme on peut s'y attendre, en raison de leur relation étroite avec la sphère génitale et de leur radiosensibilité, ce sont l'iléon, le côlon sigmoidien et le rectum qui sont les localisations des complications post-radiothérapeutiques les plus fréquentes et ce sont ces lésions qui nécessitent le plus souvent une correction chirurgicale. Les complications urologiques prennent la seconde place, suivies des complications gynécologiques. Les atteinTableau III—Distribution (%) des types de complications MII et CH en fonction des stades traités

Classe	Stade I (n = 343)	Stade II (n = 290)	Stade III (n = 187)	Stade IV (n = 42)
MII	25.7	23.1	21.9	21.4
CH	5.8	7.6	3.7	2.4

77 classifications sont manquantes.

Tableau IV—Distribution (%) des types de complications MII et CH en fonction de la durée de la surveillance post-thérapeutique

	Durée, ans			
Classe	1 – 2	2 – 5	5 – 10	> 10
MII	18.4	26.1	25.9	23.6
CH	2.2	10.5	6.1	4.3

Tableau V—Distribution (%) des types de complications MII et CH en fonction de la chirurgie pré- et post-radiothérapie

Classe	Absence de chirurgie (n = 757)	Chirurgie pré-radiothérapie (n = 134)	Chirurgie post-radiothérapie (n = 44)
MII	23.5	26.1	15.9
CH	5.3	5.2	15.9*

*$p < 0.001$.

Tableau VI—Distribution (%) des types de complications MII et CH en fonction de la chirurgie post-radiothérapie

		Chirurgie post-radiothérapie		
Classe	Absence de chirurgie (n = 757)	Hystérectomie totale (n = 11)	Hystérectomie radicale (n = 20)	Exentération pelvienne (n = 13)
MII	23.5	18.2	0.0	38.4
CH	5.3	0.0	20.0*	23.2*

*$p < 0.001$.

tes des gros vaisseaux et des structures osseuses et cutanées sont plus rares.

La majorité des lésions digestives et urologiques se manifestent par des subocclusions ou des occlusions des viscères. Un nombre non négligeable de celles-ci évoluent cependant vers la fistulisation. Les complications gynécologiques sont essentiellement d'ordre hémorragique et nécrotique.

Les modalités du traitement chirurgical des complications digestives sont l'objet d'une controverse dans la littérature. Les interventions de dérivation ont pour avantage de limiter les dissections extensives ce qui évite de compromettre la vascularisation déjà déficiente des anses intestinales touchées par la radiothérapie.[7,25,26,37] Se basant sur le fait que les dérivations n'empêchent pas la progression de la radio-entérite et que, par conséquent, elles ne mettent pas la malade à l'abri de complications futures, d'autres auteurs préconisent des interventions de résection.[12,20] Enfin, certains croient que chaque cas devrait être individualisé.[17,24,29,32]

Dans notre série, les dérivations ont été utilisées essentiellement chez les malades pour qui une résection aurait été extensive et dangereuse. Chaque fois que cela a été possible, une résection limitée a été pratiquée pour traiter aussi bien les occlusions et les fistules que les perforations.

Les lésions du rectum ont été traitées majoritairement par colostomie de dérivation avec opération de Hartmann. Les fistules entéro-vaginales ont été traitées soit par résection soit par diversion temporaire avec interposition d'épiploon sur le foyer de la fistule.

Sur le plan urologique, on a tenté d'utiliser, chaque fois que cela était possible, l'arbre urinaire inférieur; ainsi, 10 des 16 sténoses urétérales ont pu être corrigées par urétéro-néo-cystostomie. Dans la majorité des autres cas, il a fallu recourir à des dérivations conduisant chez un tiers des patientes à des conduits iléaux.

Bien que la mortalité postopératoire (5.45%) soit relativement acceptable dans les circonstances, la morbidité a été élevée et ce en raison non seulement de la précarité des tissus opérés mais également de la malnutrition et des déficiences immunitaires dont sont atteintes la majorité de ces patientes. Plusieurs d'entre-elles ont dû subir des interventions itératives et la durée moyenne des hospitalisations a été très élevée (75.7 jours).

Enfin, 38% des 55 malades traitées sont porteuses d'une ou plusieurs stomies externes définitives.

Conclusions

Le traitement du cancer du col par radiothérapie a causé par ordre de fréquence des complications entériques, urologiques, gynécologiques, vasculaires, cutanées et osseuses chez 29.3% des 939 malades qui ont été traitées dans notre institution sur une période de 13 ans. La fréquence des complications a été directement proportionnelle à la dose de rayons administrée et la relation avec d'autres facteurs favorisants n'a été qu'indirecte.

Dans 5.9% des cas, les complications ont nécessité un traitement chirurgical. La résection du segment malade a été l'intervention de choix dans les complications digestives et urologiques et les dérivations ont été réservées aux cas où la résection n'était pas réalisable.

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Parathyroid Exploration for Primary Hyperparathyroidism

Parathyroidectomy was studied retrospectively in 107 patients with primary hyperparathyroidism. This condition was diagnosed by measuring both the total serum calcium and ultrafilterable calcium (non-protein-bound) levels. The identification of ultrafilterable calcium is an important adjunct to parathyroid surgery as it allows the diagnosis of hyperparathyroidism when the total serum calcium level is normal. The surgical technique for selective parathyroidectomy and multiple biopsies was uniform. Parathyroid adenoma was discovered in 73 patients, diffuse hyperplasia in 26 and combined disease in 8. Postoperatively, two patients suffered from permanent hypocalcemia and three had hypercalcemia.

Les résultats de la parathyroïdectomie ont été étudiés rétrospectivement chez 107 patients souffrant d'hyperparathyroïdie primaire. La maladie a été diagnostiquée par détermination de la calcémie totale de même que des taux de calcium ultrafiltrable (non lié). L'identification du calcium ultrafiltrable est une aide importante à la chirurgie parathyroïdienne car elle permet le diagnostic d'hyperthyroïdie même en présence d'une calcémie totale normale. La technique chirurgicale de parathyroïdectomie sélective ainsi que celle des biopsies multiples ont été uniformes. Un adénome parathyroïdien a été découvert dans 73 cas, une hyperplasie diffuse dans 26 cas et une maladie combinée, 8 fois. En postopératoire, deux patients ont été atteints d'hypocalcémie permanente et trois ont présenté une hypercalcémie.

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Surgery of the parathyroid glands for primary hyperparathyroidism is controversial. The preferred surgical technique varies[1-3] and the histologic findings are often difficult to interpret by even the most skilled pathologist.[4] We review retrospectively 107 patients who had parathyroid exploration for primary hyperparathyroidism to study the diagnostic methods used, the reliability of accurate measurements of total and ultrafilterable serum calcium levels, the results following a uniform surgical approach and the histologic findings.

Patients and Methods

During a 20-year period, the senior author (J.R.M.) performed parathyroidectomy on 107 patients with a diagnosis of primary hyperparathyroidism. As in most series, women were affected more often than men. There were 79 women (average age 56 years) and 28 men (average age 45 years).

The principal clinical features of this disorder were renal stones (44 patients), bone disease comprising osteoporosis and osteitis fibrosa (44 patients), constitutional symptoms that included fatigue, lassitude, anorexia, depression and generalized pain (51 patients), and gastrointestinal complaints—peptic ulcer, indigestion, constipation (26 patients). In 13 cases, unsuspected hypercalcemia was discovered during routine biochemical screening.

The surgical technique was similar in all cases. Through a collar incision, careful exploration identified the parathyroid tissue in a bloodless field. A small segment was excised from each parathyroid gland encountered and sent for immediate histologic study. Parathyroid adenomas were completely removed and normal glands left in situ unless they were abnormally large. When all the glands were hyperplastic, they were excised, leaving a glandular remnant with an estimated mass of 40 to 60 mg. Glands, or portions thereof left in situ, were marked with black silk sutures in case re-exploration was necessary later.

We disagree with the practice of discontinuing exploration if an adenoma along with one normal gland is found, because there is ample evidence that multiple adenomas can exist.[5,6] Further, we do not concur that if two glands are hyperplastic, then all glands must be so.[7] Subtotal parathyroidectomy as advocated by Paloyan and associates[3] was not performed routinely. Our surgical technique was similar to that of Clark and colleagues[8] in which all glands are identified and selective excision is performed.

We did not localize glands by arteriography, selective venous sampling or toluidine blue staining. In recent years tomography and ultrasonography have localized enlarged glands in some patients but use of these techniques does not preclude thorough surgical exploration.

Diagnosis

The presence of a calcium research laboratory at the Kingston General Hospital permitted accurate measurements of total serum calcium and ultrafilterable calcium (non-protein-bound) levels. The diagnosis of hyperparathyroidism was based on the demonstration of elevated total serum and or ultrafilterable serum calcium levels with the exclusion of other causes of hypercalcemia. The upper limits of normal in this laboratory (for both sexes) for total serum calcium and ultrafilterable serum calcium are 2.54 mmol/L and 1.46

mmol/L respectively. Measurement of urinary cyclic adenosine monophosphate excretion (immunoassay kit supplied by New England Nuclear, Boston, Mass.) and serum immunoreactive parathyroid hormone (immunoassay kit supplied by Nichols Institute Diagnostics, San Juan Capistrano, Calif.) were of limited diagnostic value.

Operative Findings

Adenoma was discovered in 73 patients (including one adenocarcinoma), diffuse hyperplasia in 26 and combined adenoma and hyperplasia of the parathyroid glands in 8. In the eight patients with hyperplasia, glands were diagnosed as normal on microscopic examination of frozen sections, but focal nodules of hyperplasia were evident on examination of the permanent sections.

Surgical exploration identified 84% of the glands in 102 patients (assuming an average of four parathyroid glands per patient); more than four glands were found in the other 5—five glands in 4 of them and eight glands in the fifth. The anatomic locations of the glands, especially the inferior pair, were highly variable, as reported by others.[9] Ectopic glands were found in the thyroid glands, the thymus gland, the carotid sheath, on the lower trachea, posterior to the esophagus, in the posterior superior mediastinum and retrosternally. In one case there were bilateral adenomas and, in another, five discrete adenomas were located within one parathyroid gland, confirming that multiple parathyroid adenomas do exist,[5] although they are not common. The 1.9% incidence of multiple adenomas in this series is similar to the 1.9% incidence described by Verdonk and Edis.[6] The adenomas ranged in weight from 35 mg to 35 g.

Results

Follow-up of the 107 patients, ranging from 4 months to 20 years, revealed that two who had adenomas removed have permanent hypocalcemia. In one only two glands were found, the adenoma was completely excised and in the other, normal gland, a biopsy only was done. In the second case an adenoma was completely excised and biopsies were done on the three normal glands. These are the only cases in the series in which biopsy of normal glands could be incriminated as the cause of hypocalcemia.

Three patients remain hypercalcemic despite a second neck exploration. In one, four glands were identified. One gland that appeared grossly enlarged, but subsequently proved to be histologically normal was excised, and biopsies were done on three normal glands at the first procedure. Upon re-exploration two and one-third of the three remaining, normal-appearing glands were removed. This patient subsequently proved to have benign familial hypercalcemia. In the second patient, three glands were found: one adenoma weighing 255 mg was excised, one gland, thought to be hyperplastic on frozen section but subsequently proved normal was excised and a 40-mg remnant of a third gland, histologically normal, was left in situ. During re-exploration, a fourth gland was not found and hemithyroidectomy failed to reveal parathyroid tissue within the specimen or to alter the elevated calcium levels. In the third patient only three parathyroid glands were found; two were normal histologically and the third contained an adenoma weighing 170 mg. It seems likely that this patient has a second adenoma in a fourth gland that was not found.

There were no deaths or serious complications. Specifically, there was no case of permanent hoarseness postoperatively or major wound problems. A temporary Horner's syndrome was noted in one and a small pneumothorax in two patients.

Other biochemical diagnostic methods were not as accurate as the ultrafilterable serum calcium level. Measurement of urinary cyclic AMP excretion resulted in 13 of 22 patients having surgically proven parathyroid adenomas. This was especially true in patients with mild hypercalcemia (total serum calcium equal to or less than 2.7 mmol/L) and in whom urinary cyclic AMP excretion was normal (12 of 16). However, cyclic AMP excretion was elevated in five of six patients in whom total serum calcium levels exceeded 2.7 mmol/L. Measurement of serum immunoreactive parathyroid hormone was likewise proven of limited value because normal values were found in 59% of the patients with surgically proven adenomas.

Discussion

The controversy over subtotal versus selective parathyroidectomy for hyperparathyroidism has been reported by many authors.[2,3,10,11] The policy followed in this series was that of so-called "selective" excision of parathyroid tissue, based upon the gross and microscopic appearance of the parathyroid glands at exploration.

The reported frequency of hypocalcemia after routine subtotal parathyroidectomy varies widely (Table I[2,3,8,12-14]). Paloyan and colleagues[3] reported a rate of 2%, Beahrs[15] 13% and Bruining[11] 37%. It is difficult to understand why routine subtotal parathyroidectomy should not, eventually, lead to a higher rather than a lower rate of subsequent hypocalcemia than selective excision with preservation of more of the normal parathyroid tissue.

Persistent hypercalcemia postoperatively results from failure to identify and excise enough hyperfunctioning parathyroid tissue, usually the consequence of variation in number and location of parathyroid glands.

The importance of accurate measurements of ultrafilterable serum calcium levels in diagnosing hyperparathyroidism deserves special attention. In this series 10 of the 107 patients had clinical manifestations of underlying hyperparathyroidism but normal total serum calcium levels. In each of them, the ultrafilterable serum calcium level was elevated above the normal limit of 1.46 mmol/L. Postoperatively, they had normal total and ultrafilterable serum calcium levels.

The criteria for histologic differentiation between parathyroid adenoma and hyperplasia have been questioned,[4] and frozen-section diagnosis from a tiny biopsy specimen of tissue cannot always be made with accuracy. For this reason the gross appearance of exposed parathyroid glands must be combined with the pathologist's interpretation of frozen sections, in order to make an accurate diagnosis in the operating room.

Thorough exploration of the neck is required, even if an adenoma is found

Table I—Results of Parathyroidectomy for Primary Hyperparathyroidism

Series	Technique	No. of patients	Postoperative hypercalcemia, %	Postoperative hypocalcemia, %
Paloyan and colleagues, 1973[3]	Subtotal excision	98	1.0	2.0
Palmer and colleagues, 1975[2]	Selective excision	250	1.6	1.6
Clark and colleagues, 1976[8]	Selective excision	242	0.4	2.6
Coffey and colleagues, 1977[12]	Selective excision	200	1.5	0
Ransom and colleagues, 1977[13]	Selective excision	109	5.0	3.0
Kelly, 1980[14]	Selective excision	242	1.0	2.0
Present study	Selective excision	107	2.8	1.9

early in the operation, because of the frequent association of adenoma with hyperplasia (7.8% in this series), the occasional occurrence of multiple parathyroid adenomas[5,6] and the possibility of more than four glands. Some authors believe that too thorough a search may endanger the blood supply and functional survival of normal parathyroid glands, but the occurrence of permanent hypocalcemia in this series would indicate that it is not likely to be a major problem if the operative field is kept reasonably dry and careful biopsy of these "normal glands" is performed away from the blood supply.

Complete mediastinal exploration through a sternal splitting incision was carried out only once in this series.

Our policy is to consider it necessary only after a second neck exploration, including thyroidectomy, has failed to reveal the presence of abnormal parathyroid tissue.

However, when four parathyroid glands or an adenoma cannot be found during exploration of the neck, the retrosternal tissue, including the thymus gland, is removed through the neck incision before part of the thyroid gland is excised. Parathyroid glands are occasionally found in this location and can be removed without splitting the sternum.

Our sincere thanks to the pathologists at the Kingston General Hospital and to the staff of the calcium research laboratory.

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Heart and Heart–Lung Transplantation: the Canadian and World Experience from December 1967 to September 1985

By Sept. 1, 1985, 62 centres around the world were identified as having participated in heart transplantation; of these 14 had also performed combined heart–lung transplantation. Between December 1967 and December 1984, 1599 recipients had undergone 1644 transplant procedures. By September 1985, 112 heart–lung transplant procedures had been performed in 110 patients. Overall survival at 1 and 3 years respectively, excluding perioperative mortality, averaged 80% and 65%; for heart transplantation alone survival rates were 85% and 75%, respectively.

In Canada, of 81 heart and 5 heart–lung transplant procedures that were performed in nine centres between April 1981 and September 1985, 38 heart and 2 heart–lung transplants were carried out in the first 9 months of 1985. Sixty-four of the heart and 2 of the heart–lung transplant recipient were alive from 20 days to 4.42 years postoperatively.

Au 1er septembre 1985, 62 établissements de par le monde avaient été identifiés comme ayant participé à des greffes cardiaques; parmi ceux-ci, 14 avaient aussi réalisé des greffes coeur–poumons. De décembre 1967 à décembre 1984, 1599 receveurs avaient subi un total de 1644 greffes. En septembre 1985, 112 greffes coeur–poumons avaient été pratiquées chez 110 patients. A l'exclusion des décès peropératoires, la survie globale à 1 et 3 ans a été en moyenne de 80% et 65% respectivement; pour les greffes cardiaques seules, ces taux étaient respectivement de 85% et 75%.

Au Canada, sur 81 greffes cardiaques et 5 greffes coeur–poumons pratiquées dans neuf établissements entre avril 1981 et septembre 1985, 38 greffes cardiaques et 2 transplantations coeur–poumons ont été réalisées au cours des 9 premiers mois de 1985. Soixante-quatre greffés cardiaques et 2 receveurs de greffes coeur–poumons ont survécu de 20 jours à 4.42 années après leur opération.

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The pioneering efforts of Shumway and Lower in the late 1950s and the 1960s resulted in the development of surgical techniques for both heart and heart–lung transplantation that routinely allowed animal survival intra- and postoperatively.[1] Extended survival was then achieved following heart transplantation by immunosuppressing the animals with azathioprine and prednisone.[2] A reliable method of determining organ rejection based on a 20% decrease in cumulative electrocardiographic voltage was recognized and, finally, a means of reversing rejection episodes with pulsed doses of steroids was developed.[3,4] These efforts provided the experimental basis for human-to-human heart transplantation.[5]

Stimulated by the first few cardiac transplant procedures, nearly 50 other centres around the world undertook cardiac transplantation, with little preparation beyond the surgical technique itself. Over 100 transplants were performed in 1968 alone and 250 by the end of 1970. With the death of most recipients because of infection or rejection, initial enthusiasm waned and most centres abandoned heart transplantation.

Over the ensuing decade, only five centres continued heart transplantation. By the end of the 1970s, new diagnostic and management strategies had been developed, leading to improved survival, particularly at Stanford University Medical Center, and with the introduction of cyclosporine immunosuppression in December 1980, a renaissance in cardiac transplantation occurred around the world. Despite three initial failures of combined heart–lung transplantation in the late 1960s and early 1970s, heart–lung transplantation was successfully restarted clinically by Reitz and colleagues.[6].

Since the introduction of cyclosporine for clinical cardiac transplantation, 62 centres worldwide have participated in heart or heart–lung transplantation in 1599 recipients.

The information for this report derives from the International Heart Transplantation Registry,[7] the Canadian Heart Transplantation Registry, personal communication with the 9 Canadian centres that have active heart transplant programs, the 14 centres pursuing combined heart and lung transplantation, and the recent literature.

The report reviews experience in heart transplantation from December 1967 to December 1984 (world experience) and until September 1985 (Canadian experience), and in heart–lung transplantation from March 1981 to September 1985.

Overview

The number of centres performing heart transplantation alone or heart and heart–lung transplantation numbers 55 according to the International Heart Transplantation Registry[7] (62 by personal communication). Of the 62 centres, 39 are in the United States, 9 in Canada and 14 elsewhere.

Fifty-five centres in nine countries performed 1644 transplants in 1599 recipients between December 1967 and December 1984. One thousand patients received new organs in the United States, 53 in Canada and 546 elsewhere. The near-exponential rise in transplantation is illustrated by the fact that 44.6% (713 patients) of all transplant procedures were performed in 1984.

The predominant age group for recipients ranged from 35 to 55 years. Ten recipients were younger than 10 years and 9 older than 60 years (Fig. 1).

Cyclosporine was used for immunosuppression in 1014 of the recipients. Figure 2 compares actuarial survival for 120 patients who underwent cardiac transplantation with (46 patients) and without (74 patients) cyclosporine immunosuppression, excluding those who died within 30 days of operation. At 3 years, 74% of recipients who had cyclosporine immunosuppression versus 47% of those who did not, remained alive. In order to achieve more homogeneous groups of patients, the above data were re-analysed for only those patients transplanted after 1978. If

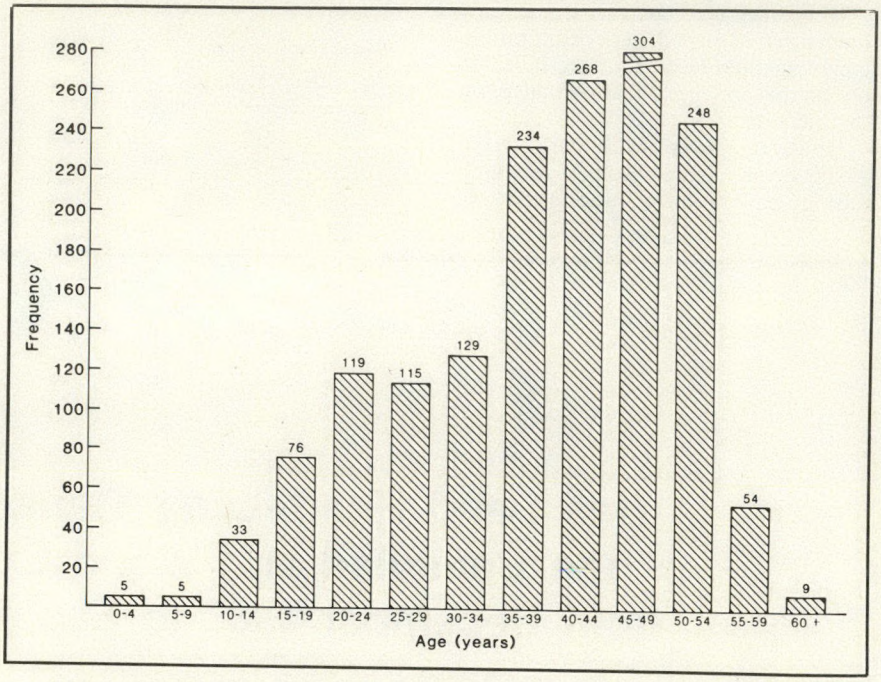

FIG. 1—Age of 1599 patients who underwent heart or heart–lung transplantation between December 1967 and December 1984; 1339 (83.7%) were men and 260 (16.3%) were women.

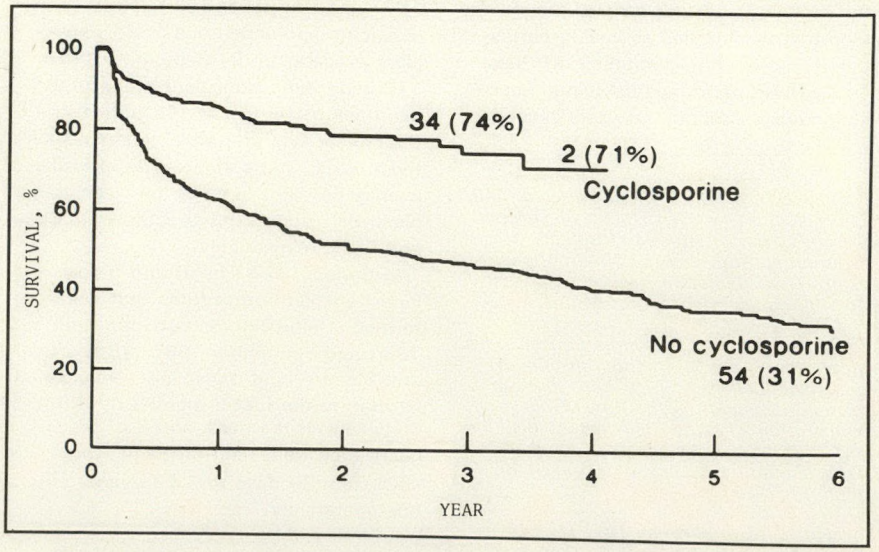

FIG. 2—Actuarial survival of 120 patients who underwent heart transplantation with and without cyclosporine immunosuppression ($p < 0.0001$). (Reproduced by permission from Kaye MP, Elcombe SA, O'Fallow WM: *J Heart Transpl* 1985; 4: 290–292.)

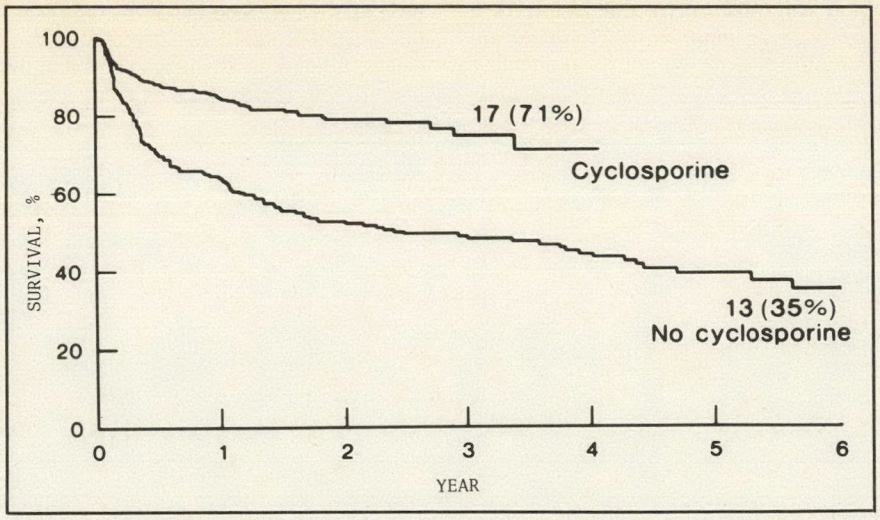

FIG. 3—Actuarial survival of patients who underwent heart transplantation with and without cyclosporine immunosuppression during and after 1978. Deaths within 30 days of operation are excluded. (Reproduced by permission from Kaye MP, Elcombe SA, O'Fallow WM: *J Heart Transpl* 1985; 4: 290–292.)

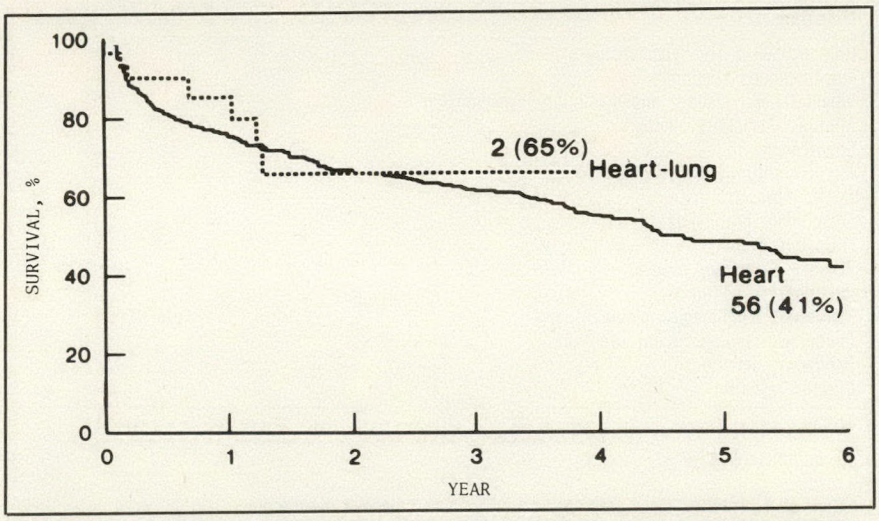

FIG. 4—Actuarial survival of patients who underwent heart or heart–lung transplantation. Survival 1 and 2 years after heart–lung transplantation is comparable to that of heart transplantation alone. (Reproduced by permission from Kaye MP, Elcombe SA, O'Fallow WM: *J Heart Transpl* 1985; 4: 290–292.)

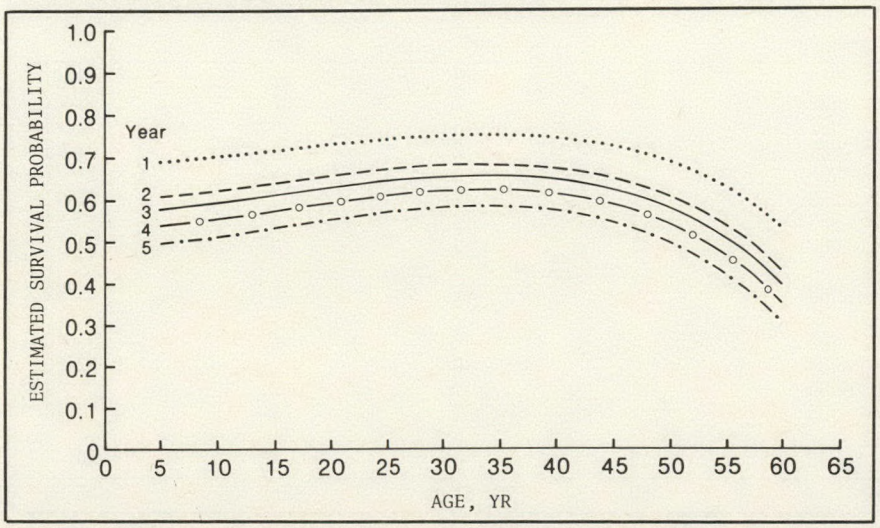

FIG. 5—Probability of surviving 1, 2, 3, 4 or 5 years after transplantation for recipients ranging in age from 5 to 60 years.

mortality in the first 30 days is again excluded, 3-year survival still remains significantly ($p < 0.0001$, Mayo computer main-frame) improved with cyclosporine therapy (Fig. 3). Figure 4 illustrates that 1- and 2-year survival rates following combined heart and lung transplantation are comparable to those of heart transplantation alone.

From a study of the effect of age on survival following cardiac transplantation at centres where more than 20 transplant procedures have been performed, the International Registry for Heart Transplantation developed a proportional-hazards model involving age and cyclosporine use to determine the probability of survival for recipients using cyclosporine for immunosuppression by their age at the time of transplantation (Fig. 5). Because of the small number of patients at 4 and 5 years, caution must be used in interpreting the apparent dip in all survival curves that may relate simply to extrapolation of the mathematical model. While these curves represent the means of data generated by a number of centres, the goal of any transplant program must be to perform better than the best, which at this time is Stanford University Medical Center (Fig. 6).

Heart Transplantation in Canada

In 1968 and 1969, 20 cardiac transplant procedures were performed in Ontario and Quebec. Most patients died of infection or rejection within 1 year, but one patient from Quebec survived over 4 years before dying of rejection and a cerebrovascular accident and one patient from Ontario survived over 5 years. From 1970 until 1980, no further cardiac transplant procedures were performed in Canada, but in April 1981, Dr. Neil McKenzie at the University Hospital in London, Ont., reintroduced cardiac transplantation, and in May 1983 he performed Canada's first

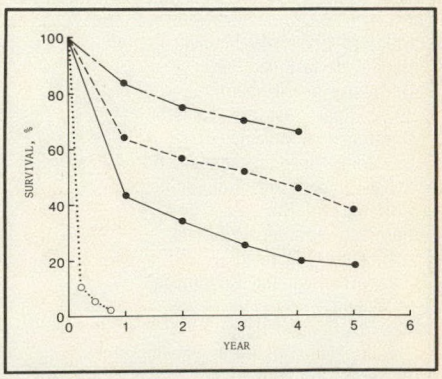

FIG. 6—Actuarial survival for patients who underwent heart transplantation at Stanford University Medical Center (including perioperative mortality). ○ = not transplanted, ——— = January 1968 to December 1973, - - - - = January 1974 to December 1980, — - — = December 1980 to May 1985.

combined heart and lung transplantation. Table I summarizes the subsequent developments in this country. Excluding the 20 transplants performed before 1970, 81 heart transplants in 80 recipients and 5 combined heart–lung transplants have been performed. The age of the recipients has ranged from 12 to 60 years.

The indications for heart transplanta-

Table I—Heart Transplantation in Canada: April 1981 to September 1985

Centre	Start of program	Patients transplanted M	F	Total	Age range, yr
University Hospital, London, Ont.	4/81	33	6	39†	12–58
Hôpital Notre-Dame, Montreal	7/82	9	3	12	21–48
Institut de Cardiologie de Montreal	4/83	8	4	12	17–52
Hôpital Sainte-Justine, Montreal	1/84	1	0	1	15
University of Ottawa Heart Institute	5/84	5	1	6	30–51
Toronto General Hospital	6/84	2*	0	2	32, 60
Royal Victoria Hospital, Montreal	1/85	5	1	6	42–56
Toronto Western Hospital	3/85	2	0	2	26, 37
University of Alberta Hospitals, Edmonton	7/85	2	0	2	41, 53
Totals		65	15	80	

*Heart–lung procedures.
†1 patient underwent a second procedure giving a total of 81 transplants in 80 patients.

Table II—Indications for Transplantation

Indication	No. of procedures
Cardiomyopathy	38
Ischemic heart disease	37
Valvular heart disease	4
Idiopathic hypertrophic subaortic stenosis	1
Rejection	1
Total	81

Table III—Survival* and Rehabilitation

Feature	No. (%)
Transplantations	80
Currently alive	64 (80.0)
Fully rehabilitated	54 (84.4)
Partially rehabilitated	9 (14.1)
Not rehabilitated	1 (1.6)

*Duration of survival ranged from 20 d to 4.42 yr.

Table V—Indications for Heart–Lung Transplantation

Indication	No. of procedures
Primary pulmonary hypertension	49
Eisenmenger's syndrome	44
Valvular heart disease and pulmonary hypertension	1
Multiple pulmonary emboli	1
Emphysema*	3
Alpha-1 antitrypsin deficiency*	3
Cystic fibrosis†	2
Eosinophilic granuloma	1
Fibrosing alveolitis†	1
Primary pulmonary fibrosis	1
Pulmonary asbestosis†	1
Pulmonary lymphangioleiomyomatosis‡	1
Pulmonary staphylococcal infection	1
Pulmonary sarcoidosis	1
Chronic rejection*§	2
Total	112

*1 patient still alive.
†Died.
‡Died at 23 months from progressive fibrosis and bronchial obstruction.
§2 patients underwent second procedure, giving 112 transplant procedures in 110 patients.

Table IV—Heart–Lung Transplantation: World Experience March 1981 to September 1985

Centre	Start of program	Patients transplanted M	F	Total	Age range, yr
Stanford University Medical Center	3/81	17	10	27*	19–45
Hôpital de la Pitie, Paris	3/82	5	2	7	18–42
University of Pittsburgh	5/82	11	15	26†	12–45
Texas Heart Institute, Houston	7/82	2	2	4	38–55
University of Munich	2/83	2	0	2	21–27
University Hospital, London, Ont.	5/83	1	2	3	35–47
Johns Hopkins Hospital, Baltimore	7/83	3	1	4	20–35
University of Brussels	8/83	1	2	3	24–
Harefield Hospital, Harefield, Middlesex, England	12/83	9	12	21	3.5–52
Papworth Hospital, Cambridge, England	4/84	1	4	5	30–40
Toronto General Hospital	6/84	2	0	2	32–60
Arizona Heart Institute, Phoenix	12/84	1	1	2	39–42
University of Capetown	2/85	1	2	3	20–28
Hanover Medical School, Hanover, W. Germany	4/85	0	1	1	40
Totals		56	54	110	3.5–60

*1 patient underwent a second transplantation, giving 28 transplant procedures in 27 patients.
†1 patient underwent a second transplantation, giving 27 transplant procedures in 26 patients.

tion in Canada are outlined in Table II and, like most other centres, include predominantly cardiomyopathy and ischemic heart disease.

Table III summarizes the survival and rehabilitation data in the 80 heart-transplant recipients. Meaningful actuarial survival curves cannot be generated owing to the relatively small number of patients and because 38 (41.5%) of the 80 received heart transplants in the first 9 months of 1985. Nevertheless, 64 (80%) patients are alive from 20 days to 4 years and 4 months after transplantation. Of these, 54 (84.4%) are fully rehabilitated (i.e. follow-up longer than 3 months back at work or carrying out preoperative activities, or capable of returning to work or carrying out preoperative activities). For 9 (14.1%) of the 64 patients the follow-up is less than 3 months and 1 patient has no rehabilitation potential.

Sixteen recipients died — of rejection (3), infection (2), right ventricular failure (3), respiratory failure (3), "stone heart" (2), pancreatitis (1), thrombotic thrombocytopenia (1) and myocardial infarction (1).

Heart–Lung Transplantation: World Experience

Combined heart and lung transplantation was first performed in 1969; by the end of 1971 three such procedures had been performed, with the longest survival being only 23 days.[8–10] All patients died of infection or bronchial disruption, or both. No further heart–lung transplants were performed until March 1981, when Reitz and Shumway, stimulated by success in the laboratory with primates and immunosuppression with cyclosporine in clinical cardiac transplantation, performed the first clinically successful combined heart–lung transplant in a 45-year-old woman, who is still alive and well 4.5 years later.[6]

One year elapsed before another centre, La Pitie in Paris, followed the Stanford lead. Table IV summarizes results from the 14 transplantation centres that have carried out heart–lung transplantation. Between March 1981 and September 1985, 56 males and 54 females, ranging in age from 3.5 years to 60 years, have undergone a total of 112 procedures.

The indications for these 112 procedures are outlined in Table V. The predominant indicators were primary pulmonary hypertension and Eisenmenger's syndrome.

A most interesting group of patients, those with primary lung parenchymal disease (i.e., cystic fibrosis, emphysema) accounts for only a small proportion of the recipients to date but represents a huge reservoir of potential candidates. The ultimate utility of combined heart–lung transplantation for the management of patients with primary nonvascular lung disease in unknown, and only 6 of 17 such patients remain alive.

Table VI reviews the survival and degree of rehabilitation achieved in the 110 transplant patients. Of these, 59 (53.2%) patients are alive from 17 days to 4 years and 5 months after the procedure. Actuarial survival data are not available for the entire group, but 70% at 3 years is the survival rate for patients transplanted at Stanford University Medical Center (personal communication).

Overall, of the patients currently alive 48 (81.4%) are fully rehabilitated, 10 (16.9%) are partially rehabilitated and 1 (1.6%) has no opportunity for rehabilitation.

That heart–lung transplantation represents a more complex and technically difficult procedure than heart transplantation is reflected in the large number of patients who have died of multisystem organ failure, often related to hemorrhage perioperatively. The cause of death in 52 patients is summarized in Table VII.

Overall survival and quality of life following cardiac transplantation have been greatly improved since the introduction of cyclosporine immunosuppression. The most up-to-date information from the Registry of the International Heart Transplantation Society (December 1985) indicates 1- and 4-year survival rates of 90% and 80% respectively, although the results for heart–lung transplantation are not quite as good. Some centres have reported a 90% 4-year survival, including patients older than 50 years.

With over 114 centres around the world (December 1985) actively performing heart or heart–lung transplantation, it is likely that throughout the next decade cardiac-transplant patients will enjoy a quality of life comparable to that of the normal population, and the results of heart–lung transplantation will improve accordingly.

Table VI—Heart–Lung Transplantation: Survival and Rehabilitation*

Feature	No. (%)
Transplantation	110
Currently alive	59 (53.6)
Fully rehabilitated	48 (81.4)
Partially rehabilitated	10 (16.9)
Not rehabilitated	1 (1.7)

*Duration of survival ranged from 17 d to 4.42 yr.

Table VII—Heart–Lung Transplantation: Cause of Death in 51 Recipients

Cause of death	No. of patients
Infection	19
Multisystem organ failure + postop bleeding	15
Acute respiratory failure	5
Tracheal dehiscence	2
Cerebral edema + infection	2
Renal failure	2
Myocardial infarction	1
Tracheo-aortic fistula	1
Respiratory failure: donor–recipient mismatch	1
Respiratory failure due to chronic rejection	1
Liver failure	1
Lymphoma	1

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NOVANTRONE*

Mitoxantrone Hydrochloride Injection

For Intravenous Infusion Only

ANTINEOPLASTIC

CAUTION

NOVANTRONE* IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS SHOULD BE TAKEN AT FREQUENT INTERVALS PRIOR, DURING AND POST THERAPY. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED PRIOR ANTHRACYCLINES, PRIOR MEDIASTINAL RADIOTHERAPY OR WITH PRE-EXISTING CARDIAC DISEASE.

PHARMACOLOGICAL ACTION

Although its mechanism of action has not been determined, mitoxantrone is a DNA-reactive agent. It induces nuclear aberrations with chromosome scattering in cell cultures (human colon carcinoma line) and is a potent inhibitor of RNA and DNA synthesis. Compared on an equimolar basis, mitoxantrone is seven times more potent than doxorubicin in inhibiting the uptake of ^{3}H-uridine and four times more potent in inhibiting the uptake of ^{3}H-thymidine by mouse lymphoma L5178Y cells in vitro.

INDICATIONS

NOVANTRONE* is indicated for chemotherapy in patients with carcinoma of the breast, including locally advanced and metastic disease. Also for relapsed adult leukemia and lymphoma patients with hepatoma.

CONTRAINDICATIONS

NOVANTRONE* is contraindicated in patients who have demonstrated prior hypersensitivity to anthracyclines.

WARNINGS

Since NOVANTRONE* produces myelosuppression [see ADVERSE EFFECTS], it should be used with caution in patients in poor general condition or with pre-existing myelosuppression.

Cases of functional cardiac changes, including congestive heart failure and decreases in left ventricular ejection fraction have been reported. These cardiac events have occurred almost exclusively in patients who have had prior treatment with anthracyclines, prior mediastinal radiotherapy or with pre-existing heart disease. Cardiac monitoring is advisable in such patients. It is suggested that cardiac monitoring also be performed in other patients during therapy exceeding 160 mg/m^2 (approximately 12 courses) of NOVANTRONE*, as experience during prolonged treatment is limited.

NOVANTRONE* may impart a blue-green colouration to the urine for 24 hours after administration, and patients should be advised to expect this during active therapy. A reversible blue coloration in the sclerae has been reported in two cases. Safe use of NOVANTRONE* in pregnancy has not been established. No information is available concerning the presence of NOVANTRONE* in the milk of nursing mothers. Safety for intrathecal use of NOVANTRONE* has not yet been established.

PRECAUTIONS

Full blood counts should be undertaken serially during a course of treatment. Dosage adjustments may be necessary based on these counts [see DOSAGE section].

It is recommended that NOVANTRONE* not be mixed in the same infusion with other drugs. [See DRUG COMPATIBILITY section].

ADVERSE EFFECTS

NOVANTRONE* is clinically well tolerated, demonstrating a low overall incidence of adverse events, particularly those of a severe, irreversible or life-threatening nature.

Some degree of leucopenia is to be expected following recommended doses of NOVANTRONE*. With dosing every 21 days, suppression of WBC counts below 1000/mm^3 is infrequent; leucopenia is usually transient, reaching its nadir at about 10 days after dosing, with recovery usually occurring by the 21st day. Thrombocytopenia can occur, and anaemia occurs less frequently. Myelosuppression may be more severe and prolonged in patients having had extensive prior chemotherapy or radiotherapy or in debilitated patients.

The most commonly encountered side effects are nausea and vomiting, although in the majority of cases these are mild (WHO Grade 1) and transient. Alopecia may occur, but is most frequently of minimal severity and reversible on cessation of therapy.

Other side effects which have occasionally been reported include allergic reactions (one with anaphylaxis), abdominal pain, amenorrhoea, anorexia, constipation, diarrhoea, dyspnoea, fatigue, weakness, fever, gastrointestinal bleeding, stomatitis/mucositis, and non-specific neurological side effects. Tissue necrosis following extravasation has been reported rarely.

Changes in laboratory test values have been observed infrequently, e.g., increased liver enzyme levels, elevated serum creatinine and blood urea nitrogen levels (with occasional reports of severe impairment of hepatic function in patients with leukemia).

Cardiovascular effects, which have only occasionally been of clinical significance, include decreased left ventricular ejection fraction (determined by ECHO or MUGA scan), EKG changes and acute arrhythmia. Congestive heart failure has been reported. Such cases generally responded well to treatment with digitalis and/or diuretics. In patients with leukemia there is an increase in the frequency of cardiac events, the direct role of NOVANTRONE* in these cases is difficult to assess, since most patients had received prior therapy with anthracyclines and since their course is frequently complicated by anemia, fever, sepsis, and intravenous fluid therapy.

In leukemia patients treated with a single course of 12 mg/m^2 I.V. daily x 5 days, the following drug-related toxicities occured: moderate or severe jaundice or hepatitis in 8%, moderate nausea or vomitting in 8%, moderate or severe stomatitis/mucositis in 9-29%, diarrhea in 9-13%, and moderate or severe alopecia in 11%.

CLINICAL RESULTS

Introduction

Clinical trials experience has established the dosage range, efficacy and safety profile of NOVANTRONE.

A single dose can be given intermittently every three or four weeks. The recommended initial treatment dose in good risk patients is 14 mg/m^2.

Efficacy

Breast

Efficacy data are available on 349 patients with locally advanced or metastatic breast carcinoma. Results are dependent on many predisposing factors including prior chemotherapy and/or radiotherapy, the health of the patients, sites of metastases, and dose of the agent employed. In a European multi-centre first-line single-agent trial using an initial dose of 14 mg/m^2, the overall response rate was 39%, which compared favourably to doxorubicin therapy at a dose of 60-75 mg/m^2 when given to patients with similar stage disease. In an ongoing study of a direct comparison with doxorubicin, given as second-line therapy to breast cancer patients who failed a standard first-line combination, response rates are 27% for NOVANTRONE and 23% for doxorubicin. The mean duration of response observed after NOVANTRONE was greater than those reported after doxorubicin. Responses have been seen in all major sites of metastases including lymph nodes, lung, bone, skin and viscera, in patients both with and without prior hormonal therapy. Available data suggest that NOVANTRONE is comparable in efficacy with doxorubicin in the treatment of advanced breast cancer. Myelosuppression with 21-day treatment intervals is comparable with that observed with doxorubicin. Multiple courses of single-agent NOVANTRONE therapy, in some cases for longer than twelve cycles, have been administered with excellent tolerance and a good response. NOVANTRONE showed incomplete cross-resistance with doxorubicin since responses have been observed in patients in whom doxorubicin had failed or who relapsed after response to that drug. A continuing large-scale clinical trials program with combination therapy also demonstrated early positive results for efficacy and safety. In seven studies, over 100 cycles of combination therapy have been given to 77 patients.

Additional Indications

A total of 966 patients have been treated with NOVANTRONE* for three other indications of which 259 patients had non-Hodgkin's lymphona (NHL). 546 had leukemia, and 161 had hepatocellular carninoma (HCC). The following summarizes the accrual of these 966 patients:

Indication	Lederle-Sponsored Studies (No. Treated)	Independent Studies Reported in the Literature (No. Treated)
NHL	186	73
Leukemia (including pediatric cases)	282	264
HCC	75	86
	543	423

NON-HODGKIN'S LYMPHOMA. Three key studies evaluated *single agent* NOVANTRONE* in 148 patients with relapsed or refractory advanced NHL at a dose of 14 mg/m^2, IV, every 3 weeks. Of 127 patients evaluable for response in two trials, there were 10 complete responses (CR) and 42 partial responses (PR) producing an overall therapeutic response rate of 41%. The median duration of responses in the multicenter study (122 evaluable patients) was 195 days. Many patients' responses lasted in excess of one year. Responses were seen in all histological subtypes of NHL. Response to NOVANTRONE* was independent of prior chemotherapy and independent of whether the patient received prior doxorubicin. This demonstrated a lack of complete cross-resistance between NOVANTRONE* and other drugs including anthracyclines.

NOVANTRONE* was evaluated in *combination* with other agents for the treatment of NHL. A total of 28 patients were treated with different regimens. A first-line comparative trial of the combination of intermediate dose METHOTREXATE with LEUCOVORIN rescue + bleomycin + doxorubicin + cyclophosphamide + vincristine + dexamethasone (m-BACOD) versus the same combination with 10 mg/m^2 NOVANTRONE* replacing doxorubicin (m-BNCOD) has shown activity: 4 PRs in 6 evaluable patients with m-BNCOD and 3 PRs in 6 with m-BACOD. The combination of NOVANTRONE* at 10 mg/m^2, daily for 3 days, + vincristine + dexamethasone (NOD) produced 3 PRs in 5 evaluable patients. A first-line comparative trial of the combination of cyclophosphamide + vincristine + prednisone + doxorubicin (CHOP) versus the same combinations with 10 mg/m^2 NOVANTRONE* replacing doxorubicin (CNOP) has only recently begun.

NOVANTRONE* at 5 mg/m^2, daily for 3 days every 3 weeks produced one CR and 2 PRs in 8 evaluable patients with NHL; ten patients were enrolled. Several other studies reported in the literature and not sponsored by Lederle support the activity of NOVANTRONE* in the treatment of NHL.

LEUKEMIA. Four key studies sponsored by Lederle evaluated *single agent* NOVANTRONE* in 181 adult patients with refractory or relapsed acute nonlymphocytic leukemia (ANLL) or chronic myelogenous leukemia in blast crisis (B-CML) at doses ranging from 8 to 12 mg/m^2, IV, daily for 5 days, every 3 weeks. A dose response effect was evident. Optimal activity was seen at a dose of 12 mg/m^2, daily for 5 days. At this dose level, there were 19 CRs in 49 evaluable adult patients with ANLL in relapse producing an overall response rate of 39%. The median duration of complete response in the largest (121 patients) single agent study was 98 days. Several patients had remissions lasting in excess of one year. There were four studies comprising 63 patients in which NOVANTRONE* was evaluated in *combination* with other agents in the treatment of leukemia. The highest complete remission rate of 49% (11 CRs in 23 evaluable patients with ANLL) was obtained when NOVANTRONE* at 10 to 12 mg/m^2, daily for 3 days, was combined with cytosine arabinoside at 100 mg/m^2 daily for 7 days. When NOVANTRONE* at 10 mg/m^2, daily for 5 days was combined with the same dose of cytosine arabinoside, it produced 2 CRs in 8 evaluable patients. Treatment of patients with acute lymphoblastic leukemia using 10 mg/m^2 NOVANTRONE*, daily for 3 days, + vincristine + prednisone produced 10 responses in 16 evaluable patients, for a response rate of 62.5%.

Activity was also seen in B-CML. Since no standard therapy exists for this disease and bone marrow is never truly normal in this disorder, both CRs and PRs were considered evidence of efficacity. The optimal dose of NOVANTRONE* was 12 mg/m^2, daily for 5 days, producing 6 responses in 17 evaluable patients.

Experience in pediatric leukemia patients is limited. Twenty-four patients were treated with 6 to 8 mg/m^2 NOVANTRONE*, daily for 5 days. There were 3 responses in 24 evaluable children.

Fourteen adult leukemia patients received 20 to 37 mg/m^2 NOVANTRONE* once every two weeks. No therapeutic responses were observed using this schedule.

Several other studies reported in the literature and not sponsored by Lederle support the activity of NOVANTRONE* in the treatment of ANLL and B-CML.

HEPATOCELLULAR CARCINOMA. Three clinical trials sponsored by Lederle have been conducted using NOVANTRONE* in the therapy of HCC. NOVANTRONE* was administered to 65 patients intravenously at 12 mg/m^2 every 3 weeks in two studies, and in one study with 10 patients at 6 to 10 mg/m^2/day by continuous hepatic artery infusion for three consecutive days, every 3 weeks. Considering the short life span of patients presenting with HCC, a response of stable disease was included along with PRs and CRs in assessing efficacy. In these three studies, the overall therapeutic response rate was 46.7% (11 CRs and PRs + 10 stable disease in 45 evaluable patients). Activity was confirmed in other studies not sponsored by Lederle. Durations of response were variable among these studies and ranged between 3 and 52 weeks.

Safety
Data on the overall safety profile of NOVANTRONE (based on 989 patients) demonstrated advantages of NOVANTRONE compared to the anthracyclines with respect to both the quality of life and the long-term safety of patients. The majority of side effects with NOVANTRONE are mild in nature. Removal of patients from NOVANTRONE treatment for reasons of toxicity has been rare in clinical studies. A number of patients have reported no side effects at all. In addition, the relatively low risk of serious side effects has permitted treatment of patients on an out-patient basis. The most common acute effects were nausea and/or vomiting (only 3.5% severe or very severe with NOVANTRONE, compared to 10-15% reported with doxorubicin), stomatitis/mucositis (only 0.3% severe or very severe with NOVANTRONE) and alopecia (only 0.9% severe or very severe, and 15% overall with NOVANTRONE compared with 85% severe or very severe and 100% overall reported with doxorubicin). Serious local reactions have been reported rarely following extravasation of NOVANTRONE at the infusion site.

With respect to myelosuppression, initial NOVANTRONE doses of 14 mg/m^2 every three weeks are well tolerated in good-risk patients. Severe degrees of myelosuppression have been rare. The median white cell nadir in a European second-line study was 2.5x10^3; in a European first-line study only 4.8% (2/42) of patients experienced a nadir of less than 1,000. The nadir usually occurs around day 10 or 11 and returns to normal baseline value by day 21, in time for the next course of treatment. After multiple courses of NOVANTRONE, white blood cell and platelet nadirs show no further decrease beyond those observed in the first few cycles, indicating no cumulative or permanent effects of NOVANTRONE on marrow reserves.

NOVANTRONE* had an exceptional safety profile and was well-tolerated by patients treated for NHL, leukemia and hepatoma, as well as for breast cancer. However, due to the pathophysiology of leukemia and the higher doses of NOVANTRONE* employed, the safety profile differed from that seen in NHL and in hepatoma (see ADVERSE EFFECTS). The most severe and life-threatening events, i.e. bleeding and infection, are well described morbid complications of acute leukemia. Many of the episodes of hepatic dysfunction were probably related to the increased bilirubin load and increased exposure to hepatitis viruses as a result of the multiple transfusions of blood products necessary in the proper treatment of this disorder.

Cardiotoxicity
Adverse cardiac experiences have been infrequent. In contrast, doxorubicin has been reported to produce chronic cardiomyopathy and irreversible congestive heart failure in up to 11% of patients given nine or more courses of that drug at the usual dose schedule (60 mg/m^2 every three weeks). Whether or not related to NOVANTRONE, only 119 cardiac-related episodes have been reported from a total data-base of more than 3,200 treated patients, including only 29 (0.9%) reports of clinical congestive heart failure, of which only one had no other known predisposing factors. The risk of cardiotoxicity is increased with prior anti-neoplastic drug or radiation therapy. In patients without predisposing factors, development of congestive heart failure with NOVANTRONE therapy is rare.

Clinical experience suggests there is no need to lower the dose for patients with existing renal or hepatic disease.

In summary, NOVANTRONE* is well tolerated and provides a better quality of life for patients compared with doxorubicin and yet shows comparable efficacy.

NOVANTRONE has been used alone or in combination in patients with or without prior chemotherapy, as well as in those who have received prior adjuvant therapy. It is less cardiotoxic than anthracyclines such as doxorubicin and thus represents a clear therapeutic advance over currently available compounds.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
There is no known specific antidote for NOVANTRONE. As would be expected from the pharmacological actions of the drug, haematopoietic, gastrointestinal, hepatic and renal toxicity may be seen, depending on the dosage given and the physical condition of the patient. The management of overdosage is symptomatic and supportive and patients should be monitored closely. (See also the sections "WARNINGS", "PRECAUTIONS" and "ADVERSE REACTIONS").

DOSAGE
Breast Cancer, Lymphoma, Hepatoma
The recommended initial dosage for use as a single agent is 14 mg/m^2 of body surface area, given as a single intravenous dose, which may be repeated at 21-day intervals. A lower initial dose (12 mg/m^2 or less) is recommended in patients with inadequate marrow reserves due to prior therapy or poor general condition.

Dosage modification and timing of subsequent dosing should be determined by clinical judgement depending on the degree and duration of myelosuppression. If 21-day white blood cell and platelet counts have returned to adequate levels, prior doses can usually be repeated. The following Table indicates a guide to dosing based on myelosuppression.

WBC AND PLATELET NADIR	TIME TO RECOVERY	SUBSEQUENT DOSING
IF WBC NADIR >1 500 AND PLATELET NADIR >50 000	RECOVERY <21 DAYS	REPEAT PRIOR DOSE OR INCREASE BY 2 mg/m^2 IF MYELOSUPPRESSION NOT CONSIDERED ADEQUATE
IF WBC NADIR >1 500 AND PLATELET NADIR >50 000	RECOVERY >21 DAYS	WITHHOLD UNTIL RECOVERY THEN REPEAT PRIOR DOSE
IF WBC NADIR <1 500 OR PLATELET NADIR <50 000	ANY DURATION	DECREASE BY 2 mg/m^2 FROM PRIOR DOSE AFTER RECOVERY
IF WBC NADIR <1 000 OR PLATELET NADIR <25 000	ANY DURATION	DECREASE BY 4 mg/m^2 FROM PRIOR DOSE AFTER RECOVERY

Combination Therapy for Breast Cancer, Lymphoma
NOVANTRONE* has been given in various combination regimens with the following cytotoxic agents for the treatment of breast cancer and lymphomas: cyclophosphamide, fluorouracil, vincristine, vinblastine, bleomycin, METHOTREXATE (standard dose or 200 mg/m^2 with LEUCOVORIN rescue) and glucocorticoids.

As a guide, when used in combination chemotherapy with another myelosuppressive agent, the initial dose of NOVANTRONE* should be reduced by 2-4 mg/m^2 below the doses recommended above for single agent usage; subsequent dosing, as outlined above, depends on the degree and duration of myelosuppression.

Dosage for Patients with Acute Leukemia in Relapse
The recommended dosage for induction is 12 mg/m^2 of body surface area, given as a single intraveneous dose daily for five consecutive days (total of 60 mg/m^2).

In clinical studies, with a dosage of 12 mg/m^2 daily for 5 days, patients who achieved a complete remission did so as a result of the first induction course.

Re-induction upon relapse may be attempted with NOVANTRONE* and again the recommended dosage is 12 mg/m^2 daily x 5.

Combination Therapy for Leukemia
NOVANTRONE*, together with cytosine arabinoside, has been used successfully for the treatment of both first line and second line patients with acute non-lymphocytic leukemia.

For induction, the recommended dosage is 10-12 mg/m^2 of NOVANTRONE* for 3 days and 100 mg/m^2 of cytosine arabinoside for 7 days (the latter given as a continuous 24 hour infusion).

If a second course is indicated, then the second course is recommended with the same combination at the same daily dosage levels but with NOVANTRONE* give for only 2 days and cytosine arabinoside for only 5 days.

If severe or life-threatening non-hematological toxicity is observed during the first induction course, the second induction course should be withheld until the toxicity clears.

Note regarding pediatric usage: Experience in pediatric patients is limited; however, complete remissions have been observed with NOVANTRONE* as single agent therapy at a dosage of 8 mg/m^2 daily for 5 days.

ADMINISTRATION OF SOLUTION
NOVANTRONE* solution should be diluted to at least 50 mL with either Sodium Chloride for Injection (USP) or 5% Dextrose for Injection (USP). This solution should be introduced slowly into the tubing of a freely-running intravenous infusion of Sodium Chloride for Injection (USP) or 5% Dextrose for Injection (USP) administered over not less than three to five minutes intravenously. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The nonvesicant properties of NOVANTRONE minimize the possibility of severe reactions following extravasation, however, tissue necrosis has been reported rarely.

NOVANTRONE should be administered by individuals experienced in the use of antineoplastic therapy.

Caution in the handling and preparation of NOVANTRONE solutions must be exercised and the use of protective eyeglasses, gloves and other protective clothing is recommended. (See "GUIDELINES FOR SAFE USE BY HOSPITAL PERSONNEL" section.)

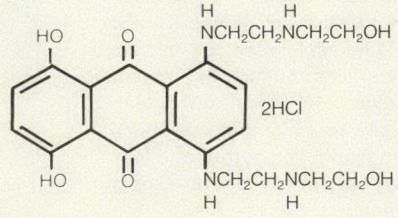
STORAGE DIRECTIONS
NOVANTRONE should be stored at room temperature–DO NOT FREEZE. With recommended storage, NOVANTRONE remains stable for two (2) years.

Following preparation of the infusion, the diluted solution should be stored at room temperature and used within 24 hours. Any original solution which remains in the vial should be discarded. *NOTE: LIKE THE ORIGINAL SOLUTIONS, THE DILUTIONS SHOULD ALSO NOT BE FROZEN.*

DRUG COMPATIBILITY
NOVANTRONE* should not be administered concommitantly with heparin since a precipitate may form. Until specific compatibility data are available, it is recommended that NOVANTRONE* not be mixed in the same infusion with other drugs.

GUIDELINES FOR SAFE USE BY HOSPITAL PERSONNEL–CONSULT THE PACKAGE INSERT.

CHEMISTRY
Composition
NOVANTRONE* mitoxantrone hydrochloride, a synthetic anthracenedione, is a potent antineoplastic agent. Its molecular formula is $C_{22}2H_{28}N_4O_62HCl$ and its molecular weight is 517.4. It is a hygroscopic dark blue solid supplied as a sterile, aqueous solution containing mitoxantrone hydrochloride equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride, sodium acetate, and acetic acid as inactive ingredients. The product does not contain antibacterial preservatives. Its structural formula appears below.



Molecular Formula: $C_{22}H_{28}N_4O_6.2$ HCl
Molecular Weight: 517.4
Chemical Name: 1,4-Dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)aminol-ethyl]amino]-9,10-anthracenedione dihydrochloride

AVAILABILITY
NOVANTRONE mitoxantrone hydrochloride injection is supplied as a sterile aqueous solution at a concentration equivalent to 2 mg mitoxantrone free base per mL, and is available in the following vial sizes:
10 mL/vial (20 mg) Product Code 9393-34
12.5 mL/vial (25 mg) Product Code 9393-72

Identification
Glass vials containing 10 and 12.5 mL of a clear, dark blue solution.

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Inguinal Intranodal Blue Nevus: a Case Report

Inguinal intranodal blue nevus is a rare lesion, but awareness of the condition will avoid a mistaken diagnosis of metastatic melanoma. The authors describe the case of a 40-year-old woman in whom an inguinal node blue nevus was discovered incidentally during radical vulvectomy for squamous cell carcinoma. They describe the characteristic light and electron microscopic features. With increased awareness of this lesion the authors believe it will be found in lymph-node chains other than the inguinal and axillary ones previously reported.

Il est rare qu'on découvre un naevus bleu dans un ganglion inguinal. Il faut en garder la possibilité à l'esprit afin d'éviter un diagnostic erroné de mélanome métastatique. Les auteurs décrivent le cas d'une patiente de 40 ans chez qui on a découvert accidentellement un naevus bleu dans un ganglion inguinal au cours d'une vulvectomie radicale pour épithélioma malpighien. Ils décrivent les caractéristiques observées aux microscopes optique et électronique. Si l'on recherche davantage cette lésion, les auteurs croient qu'elle sera identifiée dans des chaînes ganglionnaires autres que les chaînes inguinale et axillaire où elles ont déjà été signalées.

Blue nevi are uncommon pigmented lesions composed of bipolar or dendritic melanocytes and are usually found in the skin. Intranodal blue nevus was first described as a distinct pathologic entity in 1977 by Azzopardi and associates.[1] Since their report of two cases, 10 other patients with this lesion have been described.[2–8] Of these 12 patients, 10 were female and 2 male, and the axillary lymph nodes were involved in 8. We report a further case in which an inguinal lymph node was involved.

Case Report

A 40-year-old multiparous caucasian woman complained of a lesion on the vulva, present for 1 month. A 1-cm raised ulcerated lesion was seen on the inner aspect of the left labium minus and there were several smaller (up to 5 mm), slightly pigmented, macular lesions on the perineum and right labium. No enlarged lymph nodes could be palpated in either groin and no other genital tract lesions were noted. The uterus and cervix had been removed 4

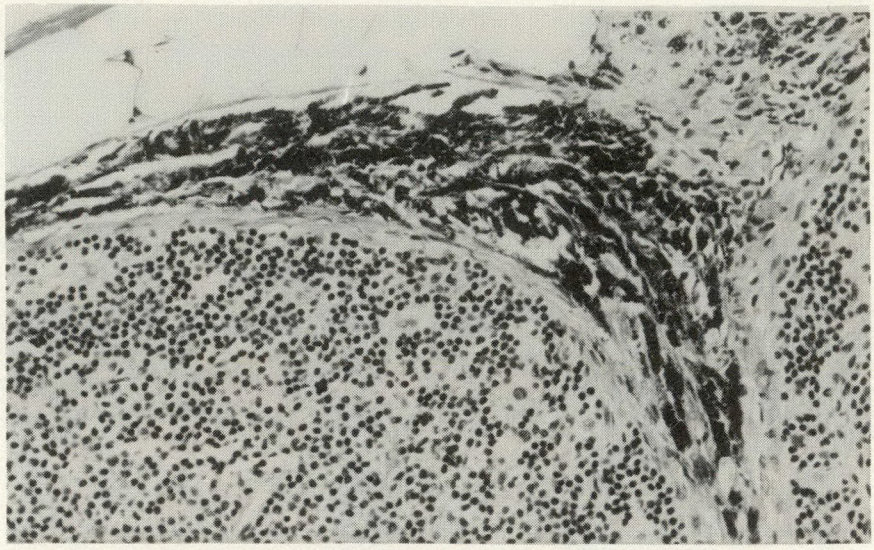

FIG. 1—Photomicrograph of inguinal lymph node containing intracapsular pigmented bipolar nevo-melanocytes (hematoxylin and eosin, original magnification × 200).

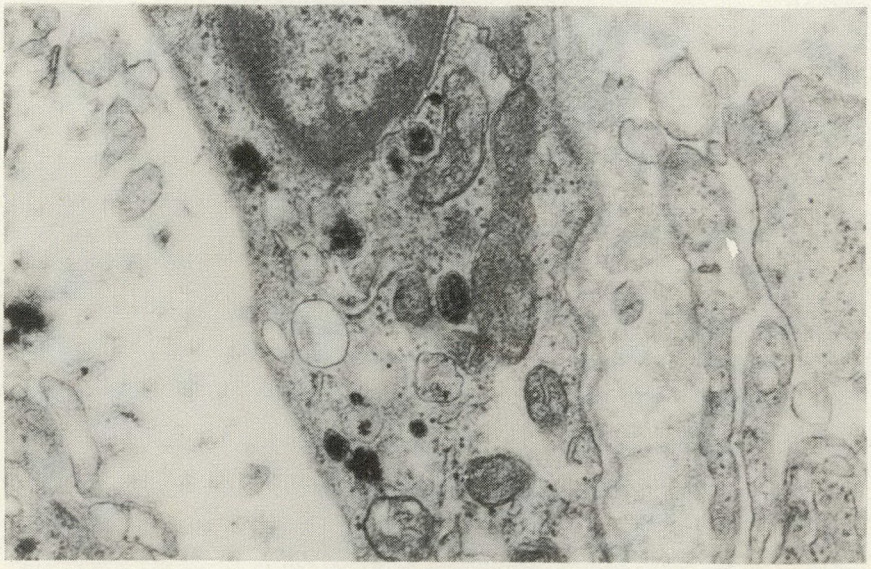

FIG. 2—Electron micrograph of nevo-melanocyte characterized by basement membrane and melanosomes at different stages of maturation (original magnification × 22 000).

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years before because of dysfunctional uterine bleeding.

Excisional biopsy of the left labial lesion was performed. Histologic examination of the specimen revealed a small area of squamous cell carcinoma with early stromal invasion arising in a background of extensive carcinoma in situ.

A radical vulvectomy was performed with en-bloc resection of the superficial inguinal lymph nodes bilaterally. During the right inguinal dissection, a single darkly pigmented lymph node, measuring 1.8 cm, was noted superficial to the cribriform fascia.

The pigmented lymph node contained elongated bipolar and dendritic cells with numerous intracytoplasmic melanin granules and some pigment-laden melanophages (Fig. 1). The pigment stained positively with Masson–Fontana stain but negatively with Ziehl–Neelsen (lipofuscin) and Prussian blue (iron) stains. The lesion involved the capsule of the lymph node, extending along the fibrous trabeculae, but it did not involve the subcapsular sinus or the nodal parenchyma. There was no necrosis or mitoses in this lesion and metastatic squamous carcinoma was not evident. Electron microscopic examination revealed a dual cell population. Some cells were elongated with a prominent basement membrane, occasional cytoplasmic processes and cytoplasmic organelles, including melanosomes at different stages of maturation (Fig. 2). In addition, prominent melanophages were seen.

No residual invasive carcinoma was present in the vulva, but there was extensive in-situ carcinoma at the margins of the previous biopsy. The smaller pigmented lesions were multifocal in-situ squamous carcinomas with features suggesting an associated condyloma virus infection. None of the other submitted lymph nodes contained melanocytes or metastatic carcinoma.

Discussion

Blue nevi are usually found in the skin, but they have also been described in the cervix,[9–13] prostate,[14] palate[15] and, more recently, in the capsule of lymph nodes.[2–8] The histogenesis is uncertain but has been discussed by Azzopardi and colleagues[1] and Epstein and associates.[6] Briefly, the intranodal blue nevus may develop from a "benign metastasis" or passive transfer of melanocytic cells from a melanocytic lesion in the region drained by the involved lymph node. Alternatively, aberrant migration of neural crest cells may explain the intranodal location. Such aberrant neurocristic cells may exhibit melanocytic or nerve-sheath differentiation,[6] the latter occurring in this case.

Although malignant transformation of a dermal blue nevus is uncommon, such an event involving an intranodal blue nevus has been postulated in patients with metastatic melanoma in whom no primary tumour could be found.[2,5,6] In a recent autopsy study a primary location could not be found in 4% of patients who died of melanoma.[16]

Eight of the 12 previously reported cases of intranodal blue nevi involved axillary lymph nodes in mastectomy specimens of women with breast carcinoma. Only two previous cases involved inguinal lymph nodes and one each a submental and popliteal lymph node.

The two inguinal intranodal blue nevi previously reported were found in a 56-year-old man who underwent surgery for varicose veins[7] and a 20-year-old woman reported to have melanoma of the foot.[8] Two of the resected inguinal lymph nodes in this woman were believed to contain metastatic melanoma. On review 10 years later both the lesion in the foot and inguinal lymph nodes were blue nevi.

Only two of the previously reported cases have involved men. The predominance of women and axillary lymph-node involvement is probably related to the frequency with which axillary lymph nodes are removed from women with breast carcinoma. We decided to report this case of a blue nevus in an inguinal lymph node because we suspect that with an awareness of this entity, further examples will be found in other lymph-node chains. Further, an enhanced awareness of this relatively rare condition by both pathologists and surgeons will avoid a mistaken diagnosis of metastatic melanoma and a futile investigation for an occult primary melanoma or even unwarranted further surgery.

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BOOK REVIEWS

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Pathologic features that might be encountered are well illustrated by the use of colour pictures taken through the sigmoidoscope, giving the visual cues of size, colour and shape. This is the best means of conveying the image of possible abnormalities of the colorectum. These pictures will be of greatest value to the primary care physician who is an occasional sigmoidoscopist. In general, surgeons will recognize the pathologic conditions based upon experience with rigid sigmoidoscopy and familiarity with surgical specimens.

This book will serve the physician-endoscopist as a reference resource for sigmoidoscopy. The index is reasonably complete, which is a primary requirement for a good reference source.

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MANUAL ON CONTROL OF INFECTION IN SURGICAL PATIENTS. 2nd ed. American College of Surgeons Committee on Control of Surgical Infections of the Committee on Pre- and Postoperative Care. Edited by William A. Altemeier (Chmn.), John F. Burke, Basil A. Pruitt, Jr. and William R. Sandusky. 388 pp. Illust. J.B. Lippincott Company, Philadelphia, 1984. $35. (US). ISBN 0-397-50575-2.

The first edition of this book, published in 1976, was a review and summary of four workshops on the control of surgical infection, organized by Dr. Altemeier between 1970 and 1972 and attended by most active investigators in this field. This edition revises and updates the first with much of the new material coming from the scientific meetings of the Surgical Infection Society, formed in 1980. The stated aim is to "provide an up-to-date, readily available source of information and guide that will be useful for the prevention and control of surgical infection in hospital practice".

This manual provides a broad, authoritative database, of value to health professionals interested in solutions to the problems of infection. The material is well organized into distinct chapters. The commentary and references are often repetitive, but this has the advantage of allowing different groups to access areas of particular interest without having to read the entire book.

Chapters dealing with definitions and classification of surgical infections, incidence and cost, epidemiology and surveillance, preoperative preparation of the patient, preparation of the operating team (attire and surgical scrub), preparation and maintenance of a safe operating-room environment, hospital design requirements for safe surgery, housekeeping techniques, laboratory support, sterilization and isolation, provide practical, state-of-the-art, authoritative information. These chapters are probably of greatest interest to operating-room nurses and supervisors, infectious-disease specialists, infection-control committees,

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Immune Response After Gastric Bypass and Weight Loss

The immune response of 22 morbidly obese patients was measured before and 6 months after gastric bypass. In-vivo skin testing was carried out using five recall antigens. In-vitro response assessed the ability of isolated lymphocytes to take up radioactive thymidine after culture with the same antigens. The mean (± SD) preoperative weight of the patients of 122 ± 14 kg declined by 33.5 ± 8 kg after 6 months. The number of positive skin tests increased from a mean (± SEM) of 1.8 ± 0.17 to 2.1 ± 0.17 (p = 0.2). Mean (± SEM) induration of the skin-test response assessed at 24 hours after antigen injection increased from 4.7 ± 0.6 mm to 5.5 ± 0.6 mm (p = 0.35) and at 48 hours from 5.4 ± 0.7 mm to 6.9 ± 0.9 mm (p = 0.05). One patient who was anergic before gastroplasty responded normally 6 months later after substantial weight loss. In-vitro response, expressed as a stimulation index (± SEM), increased from 4.71 ± 0.65 to 7.95 ± 1.56 (p = 0.06) for the average of all antigens and from 12.85 ± 2.05 to 15.79 ± 2.84 (p = 0.2) for the largest response. The authors conclude that the response to test antigens in vitro and in vivo is not reduced significantly 6 months after gastric bypass and profound weight loss. Patients with severe vomiting, rapid weight loss or sepsis may respond differently and require individual assessment.

La réponse immunitaire de 22 patients souffrant d'obésité pathologique a été mesurée avant et 6 mois après dérivation gastrique. Une intradermoréaction a été pratiquée à l'aide de cinq antigènes de rappel. La réponse in vitro a évalué la capacité de lymphocytes isolés à capter la thymidine marquée après culture en présence de ces mêmes antigènes. Le poids moyen (± écart type) préopératoire des patients était de 122 ± 14 kg a été réduit de 33.5 ± 8 kg après 6 mois. Le nombre d'intradermoréactions positives a augmenté d'une moyenne (± erreur type) de 1.8 ± 0.17 à 2.1 ± 0.17 (p = 0.2). En ce qui concerne le diamètre d'induration de la réaction cutanée, la moyenne (± erreur type) après 24 heures a augmenté de 4.7 ± 0.6 mm à 5.5 ± 0.6 mm (p = 0.35) alors qu'après 48 heures elle passait de 5.4 ± 0.7 mm à 6.9 ± 0.9 mm (p = 0.05). Un patient anergique avant gastroplastie a présenté une réponse normale 6 mois plus tard après une perte de poids importante. La réaction in vitro exprimé sous forme d'indice de stimulation (± erreur type) a augmenté de 4.71 ± 0.65 à 7.95 ± 1.56 (p = 0.06) pour la moyenne de tous les antigènes, et de 12.85 ± 2.05 à 15.79 ± 2.84 (p = 0.2) pour les réactions les plus importantes. Les auteurs concluent que la réponse in vitro et in vivo aux antigènes de rappel n'est pas réduite significativement 6 mois après dérivation gastrique et perte de poids importante. Il est possible que les patients qui ont des vomissements importants, une perte de poids rapide ou une sepsie répondent différemment et nécessitent une évaluation individuelle.

Gastroplasty and gastric bypass are frequently performed for the management of morbid obesity. MacLean and associates[1] found that a substantial proportion of these patients have become malnourished postoperatively. In developing countries malnourishment is known to be associated with an impaired host immune response.[2,3] Meakins and colleagues[4,5] have used skin testing to predict postoperative complications. Since patients who undergo gastroplasty may require further operations urgently for problems such as stomal obstruction or electively for management of hernias, gallstones or dependent skin, it seemed appropriate to assess the skin-test response in a group of obese patients after gastroplasty. We chose 6 months as a suitable time for postoperative follow-up, since most weight loss occurs within this period. We evaluated the skin-test response by the techniques of Meakins and an in-vitro test of cellular immunity that has been useful in monitoring patients who have undergone transplantation.[6]

Patients and Methods

Twenty-two morbidly obese patients (2 men, 20 women) ranging in age from 20 to 60 years (mean [±SD] 41 ± 9 years) were admitted to University Hospital in London for gastric bypass. All weighed more than twice the ideal weight. A Roux-en-Y gastric bypass was done in all. At least 2 days before operation skin testing was carried out using five recall antigens (*Candida*, mumps, purified protein derivative [PPD], *Trichophyton* and Varidase); 0.1 ml of antigen was injected intradermally as described by others.[4] The area of induration was measured at 24 and 48 hours and a test considered positive if the diameter of induration was greater than 5 mm. The test was repeated 6 months after operation. A mean skin-test response was also calculated by measuring the diameter of induration for each antigen, adding the values and dividing by five. This score was calculated 24 and 48 hours after antigen injection, before and 6 months after operation.

For in-vitro testing the procedure was carried out as described previously for cell-mediated lymphocytotoxicity.[6] Before testing, 40 ml of blood was drawn from each patient. Lymphocyte separation was carried out by a Ficoll-Hypaque technique. Cells were made up to a concentration of 2×10^6 ml and suspended in tissue culture medium (RPMI) with 20% heat-inactivated autologous serum or A serum. Tests were carried out in triplicate on microtitre plates using 0.1 ml of cells and 0.1 ml of medium containing antigen, giving a final cell number of 1×10^5 cells and a serum concentration of 10%. Controls included 1×10^5 cells in 0.1 ml of 20% A serum in RPMI, 1×10^5 cells in 0.1 ml of 20% autologous serum in RPMI and 1×10^5 cells in 0.1 ml of RPMI medium only.

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Antigen dilutions were *Candida* (Bencard Allergy Service, Division of Beecham Laboratories, Weston, Ont.) 1/100 and 1/200, mumps (Eli Lilly, Co., Scarborough, Ont.) 1/200 and 1/400, PPD (Connaught Laboratories, Toronto, Ont.) 0.2 mg and 0.02 mg, *Trichophyton* 1/100 and 1/200 and Varidase (Bencard Allergy Service) 0.1 ml (5 units streptokinase and 1.2 units of streptodornase or 0.5 units streptokinase and 0.12 units streptodornase). Cells were incubated for 4 days at 37°C with 5% carbon dioxide and then pulsed with 1 μCi of ^{3}H-thymidine for 16 hours. After harvesting, each plate was counted for 5 minutes in a B counter. Blastogenic response was recorded as a stimulation index: the mean count per minute of stimulated cells divided by the mean count per minute for control cells. The test was repeated 6 months later. Twenty values were obtained for each patient at each testing since there were two dilutions of each of the five antigens and all tests were carried out in autologous and A sera. The mean of all values was obtained for each patient preoperatively and postoperatively. The changes in the largest stimulation index were also calculated for each patient, since this was assumed to be the antigen to which the patient was most sensitized preoperatively and which might show the greatest change after weight loss. The paired *t*-test was used to compare results before and after operation.

Patients were seen preoperatively and postoperatively in hospital by a dietician and given diet sheets to take home. They were followed up by their family doctor and seen monthly at our obesity clinic. High protein intake was encouraged but exact caloric intake was not assessed. Multiple vitamins containing iron were taken by all patients.

Results

The average weight of the patients immediately preoperatively was 122 ± 14 (SD) kg. Six months later the average weight had decreased to 86 ± 11 kg. Results of skin testing and in-vitro response are summarized in Table I. Response tended to increase rather than decrease postoperatively, but the change was not significant. Skin testing was considered normal or reactive if there was a positive response (induration greater than 5 mm) to two or more antigens. Response to only one antigen indicated relative anergy and no response indicated anergy. Table II compares the mean skin-test score (diameter of induration in millimetres per antigen) before and 6 months after operation. Again the response tended to improve although only the result read after 48 hours was significant ($p = 0.05$). Table III indicates the proportion of patients in each category before and after operation and Table IV shows the change in immune response relative to weight loss.

Review of clinical data revealed no unusual features except in the patient who was anergic preoperatively. He underwent a transverse gastroplasty reinforced with Marlex around a greater curve channel. An umbilical hernia was also repaired. His weight at the time of operation was 180 kg and his height 188 cm. Initial recovery was uncomplicated and he was discharged 8 days after operation. Over the next 2 months excessive vomiting was a major problem and upper gastrointestinal series with barium confirmed that the stoma was narrow and gastric emptying delayed. Within 2 months of operation he had lost 40 kg (22% of body weight). Because of continued vomiting, the gastric bypass was revised within 3 months of operation. Skin testing before reoperation showed that he was anergic. Postoperative recovery and his subsequent course were smooth. One year later his weight was 104.6 kg.

Table I—Immune Response After Gastroplasty in 22 Patients*

Measurement of immune response	Preoperative	Postoperative	p value
No. positive skin tests	1.8 ± 0.17	2.1 ± 0.17	0.2
Average stimulation index	4.71 ± 0.65	7.95 ± 1.56	0.06
Largest stimulation index	12.85 ± 2.05	15.79 ± 2.84	0.2

*Figures are mean ± standard error.

Table II—Mean Skin-Test Response per Antigen Before and After Gastroplasty*

Time of measurement after antigen injection, h	Induration diameter, mm		
	Preoperative	Postoperative	p value
24	4.7 ± 0.6	5.5 ± 0.6	0.35
48	5.4 ± 0.7	6.9 ± 0.9	0.05

*Figures are mean ± standard error.

Table III—Skin-Test Response After Gastroplasty in 22 Patients

Response	Preoperative	Postoperative
Normal	17	17
Relative anergy	4	5
Anergy	1	0

Table IV—Change in Immune Response Related to Weight Loss

Change	Preoperative	Postoperative	No. of patients	Weight loss, %
Improved response	Anergy	Normal	1	25
	Relative anergy	Normal	3	28
Same response	Relative anergy	Relative anergy	1	26
	Normal	Normal	14	29
Worse response	Normal	Relative anergy	3	24

Discussion

Our patients, who recovered from gastric bypass without complications and lost 27% of body weight in 6 months, showed no significant reduction in immune response. In fact there was a tendency for the test results to improve although the changes approached statistical significance only for the mean skin-test score 48 hours after antigen injection. Studies in a larger number of patients might show a significant increase in skin-test and in-vitro immune response for all tests. Preoperatively, many obese patients ate a poorly balanced diet high in fat and carbohydrate. Postoperatively, the diet is low in calories but should be high in protein and vitamins. The improved diet could explain the tendency for immunologic test results to improve.

The fact that four of our patients were relatively anergic before gastroplasty is surprising and unexplainable. In a group of 727 patients with a variety of health problems preoperatively, including cancer and sepsis, 18% were relatively anergic and 12% anergic.[5] In the same study, 25 morbidly obese patients all had normal preoperative skin-test results. It is not clear whether our results are due to faulty technique, since skin testing is difficult to interpret,[7] or whether our patients were abnormal before gastroplasty. Measurement of the skin-test response using seven rather than five antigens in a multitest may give a more standardized assessment of cell-mediated immunity,[8] but the small size of the reaction is difficult to read.

The one anergic patient should have been excluded from the study because of a prior gastroplasty, but he demonstrates that anergy can occur. We were fortunate that he did well following a revision gastroplasty. In retrospect he should have been placed on parenteral nutrition to counteract the excessive preoperative weight loss. The lack of skin-test response was an even stronger indication for delaying operation. Placement of a feeding tube was not possible because of a stenotic stoma, but a smaller operation such as jejunostomy would have allowed correction of his nutritional deficit before the major revision. Such procedures have proven useful after gastroplasty.[9]

Whether patients are malnourished after gastric stapling operations is a controversial matter. One study,[1] using sophisticated methods to determine the sodium to potassium ratio, showed that patients suffered serious malnutrition after gastroplasty. Another study[10] that determined body-cell mass by whole-body counting after gastric bypass showed that lean mass was preserved although temporarily reduced early after operation. Protein malnutrition does not always affect the immune response.[11] Anergy may be more important than nutritional status in predicting susceptibility to infection.[12] However, other clinical studies[13] suggested that nutritional data can predict postoperative complications.

In our study immunosuppression was not detected 6 months after gastric bypass. Testing early postoperatively might have demonstrated a change in skin-test responsiveness.[8] Although most of the weight loss occurs in the first 6 months, the most rapid loss occurs during the first 3 months, when immunologic testing might have shown a reduced response. For patients requiring emergency reoperation after gastroplasty or gastric bypass, there is no time for nutritional or immunologic assessment. When elective operations such as cholecystectomy, hernia repair or abdominal lipectomy are performed, nutritional assessment is important. For most patients clinical judgement may be as useful as immunologic testing in predicting postoperative complications.[14] For the exceptional case in which the patient has severe vomiting or excessive weight loss, skin testing may help to determine the need for parenteral nutrition and delayed operation. In some patients sepsis must be treated and abscesses drained before anergy can be corrected.[15]

In conclusion, most patients will have no detectable change in skin-test response or in-vitro tests of cellular immunity 6 months after gastric bypass and substantial weight loss. Careful dietary advice and regular follow-up are essential to maintain nutritional status and allow early detection of complications.

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SESAP V Critique

ITEM 44

Carcinoma of the pancreas is not amenable to surgical excision of the tumor for most patients. Relief of biliary and duodenal obstruction and reduction of pain are the goals of palliative operation. Percutaneous intubation of the bile duct under radiographic control relieves biliary obstruction in many patients, but does not relieve duodenal obstruction and may be associated with major morbidity related primarily to sepsis and hemorrhage.

Biliary enteric bypass via the gallbladder is possible only if gallstones are absent, the gallbladder is healthy, and the cystic duct is not obstructed. Distention of the gallbladder, which may be associated with tumor encroachment on the cystic duct, is not a reliable indication of cystic duct patency. If the gallbladder cannot be used, biliary bypass should be by choledochojejunostomy.

Obstruction of the duodenum occurs in up 30% of patients with pancreatic carcinoma. Obstruction may occur in the duodenal sweep and also in the fourth portion of the duodenum. If gastrojejunostomy is performed only for patients with established duodenal obstruction, 13% of patients not undergoing bypass subsequently develop duodenal obstruction. Whether the duodenum should be bypassed with gastrojejunostomy will require surgical judgement depending on the operative findings.

Drainage of the obstructed pancreatic duct has been described, but its value has not been demonstrated. U tubes are contraindicated for patients with pancreatic cancer and obstructive jaundice.

C

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Needle-Guided Breast Biopsy for Mammographic Abnormalities in 561 Patients

Between 1977 and 1983, 561 consecutive patients underwent 595 surgical biopsies for suspicious mammographic lesions with negative clinical correlation. The procedure consisted of preoperative needle localization, with or without immediate radiologic examination of the biopsy specimen, depending on the presence or absence of microcalcifications in the mammographic lesion. Eighty-four carcinomas were found. Of these, 60 (71%) were infiltrating carcinoma and 24 (29%) were noninvasive carcinoma. The carcinoma yield was 24.2% in the patients with lesions involving foci of microcalcifications and 9% in those lesions without calcifications. Surgical treatment of infiltrating carcinoma consisted of 39 modified radical mastectomies, 10 (25.6%) of which were associated with positive nodes, 16 partial mastectomies with axillary dissection, 3 (18.7%) of which were associated with positive nodes, and 5 wedge resections. Treatment of noninvasive carcinoma consisted of 19 partial mastectomies with axillary dissection and 5 modified radical mastectomies. None of these were associated with positive nodes. Modified radical mastectomy was used with decreasing frequency. Of the 10 patients with infiltrating carcinoma and positive axillary nodes treated by modified radical mastectomy, 7 had one to three involved nodes and 3 had four or more; of those with positive nodes treated by partial mastectomy, 1 had one to three involved nodes and 2 had four or more. These results confirm the correlation between suspicious mammographic non-clinical lesions and breast carcinoma.

De 1977 à 1983, 561 patientes consécutives ont subi 595 biopsies chirurgicales pour des lésions suspectes à la mammographie, en l'absence de corrélation clinique. L'intervention a consisté en une localisation de l'aiguille en préopératoire, avec ou sans examen radiologique immédiat du matériel de biopsie, selon que l'on avait décelé ou non des microcalcifications à la mammographie. Quatre-vingt-quatre lésions cancéreuses ont été trouvées. Parmi celles-ci, 60 (71%) étaient des cancers infiltrants et 24 (29%) des tumeurs non envahissantes. Le rendement de lésions cancéreuses était 24.2% chez les patients avec les calcifications. Dans les cas de tumeurs infiltrantes, on a procédé à 39 mastectomies radicales modifiées dont 10 (25.6%) ont mis en évidence des ganglions positifs, 16 mastectomies partielles avec dissection axillaire dont 3 (18.7%) ont été associées à des ganglions positifs et 5 résections cunéiformes. Le traitement des cancers non envahissants s'est fait, chez 19 patientes, par résection partielle avec dissection axillaire et, chez 5, par mastectomie radicale modifiée. Dans aucun cas, on n'a mis en évidence des ganglions positifs. La fréquence des mastectomies radicales modifiées est allée en décroissant. Des 10 patientes porteuses de cancers infiltrants avec ganglions axillaires positifs et qui ont subi une mastectomie radicale modifiée, 7 avaient une atteinte de un à trois ganglions, alors que 3 avaient une atteinte de quatre ganglions ou plus; parmi celles qui avaient des ganglions positifs et qui ont été traitées par mastectomie partielle, 1 avait un envahissement de un à trois ganglions et 2 avaient quatre ganglions positifs ou plus. Ces résultats confirment la corrélation observée entre les lésions suspectes à la mammographie, sans manifestation clinique, et le cancer du sein.

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Over the last 40 years there has been a trend toward conservatism in the surgical treatment of breast carcinoma, from Halsted's radical mastectomy, then modified radical mastectomy to the present-day controversial wedge resection or partial mastectomy with an axillary dissection. Also, the use of mammography by both the primary physician and in breast screening programs has increased. This, combined with the development of fine-grain film and dedicated equipment, has greatly increased the accuracy and identification of clinically nonpalpable lesions, thus posing the challenge of how to manage the patient found to have suspicious changes on mammography. In 1971, Gallagher and Martin[1] introduced the term "minimal breast carcinoma", defining it as a carcinoma less than 0.5 cm in size. However, the term has come to represent most clinically occult lesions, up to and including those 1.0 cm in size, which for years were considered to have a more favourable prognosis because of their small size and earlier detection.

Patients and Methods

Mammograms from 561 women were evaluated by one radiologist who recommended biopsy on the basis of the following criteria.

- Microcalcifications present: (a) Clusters of fine, irregular calcifications of different shapes, sizes and density. The finer the granules and the greater the number, the more likelihood there is of a malignant lesion. (b) Lace-like branching linear groups of microcalcifications that may or may not be associated with nodular densities.

- No microcalcifications: (a) Irregular nodular densities. (b) Asymmetric densities. (c) Focal structural parenchymal alterations with a fluffy or stellate appearance.

During the period January 1977 to December 1983, 595 procedures were carried out by one surgeon using a technique of needle localization as follows. In the mammography unit, just before surgery,

the lesion is noted on the preoperative films in the craniocaudal and mediolateral projections, and the distance of the lesion from the middle of the nipple is measured in both the horizontal and vertical planes on both projections. The depth of the lesion is measured on the projection in which the lesion is closer to the skin. The appropriate needle size is selected. Needles used were 25 gauge × 5/8 inch and 22 gauge × 1½ inches for more superficial lesions and 22 gauge × 3½ inches for deeper lesions. The needle is securely anchored to the skin with Steristrips and a two-view mammogram is obtained. If not sufficiently close, the needle is repositioned without complete removal and mammography is repeated. Once a satisfactory needle position has been obtained, the patient is transferred to the operating room and under general anesthesia 1.0 ml of toluidine blue is injected as the needle is withdrawn. Incisions are made in the areola where possible or along natural skin lines and the suspect, stained tissue is excised. The amount of tissue removed is minimal and the cosmetic results are excellent. Meticulous hemostasis is obtained, no reconstruction is done and drainage is not used.

If a clinically obvious carcinoma is demonstrated, quick-section examination is performed and a specimen sent for determination of estrogen and progesterone receptors. All other specimens undergo routine pathological examination. In biopsies taken because of the presence of microcalcifications the calcifications are confirmed by tissue radiography and an additional separate biopsy is done at the same time if required (as in approximately 3% of our procedures). Areas of microcalcification are tagged for the pathologist, who also has the benefit of the tissue x-ray films. Mammography of the biopsied breast is done 3 months postoperatively to verify that the suspicious lesion has been excised. This is preferably performed in the same institution as the initial procedure. Fewer than six patients required re-excision for missed lesions or inadequate excision. One patient in this group was found to have noninvasive carcinoma.

Results

The 595 biopsies yielded 84 carcinomas (14.1% of procedures or 15.0% of patients). Of these carcinomas, 60 (71.4%) were of the infiltrating type and 24 (28.6%) were noninvasive. Carcinoma was found in 49 (24.2%) of the 202 biopsies done for microcalcifications. Biopsies undertaken for lesions without microcalcifications yielded a positive result in only 9%.

Further surgical treatment consisted of the following. Of the 60 women with invasive carcinoma, 39 underwent modified radical mastectomy; 10 (25.6%) had involved axillary nodes. Sixteen had partial mastectomy with axillary dissection and 3 (18.7%) had axillary node involvement. Because they refused further treatment or because of referral back to the original surgeon, five women had wedge resection only. Thus, 13 of the 55 patients with infiltrating carcinoma at the time of detection already had axillary involvement with the clinically occult lesion.

Of the 24 patients with noninvasive carcinoma, 19 underwent partial mastectomy with axillary dissection and 5 had a modified radical mastectomy. None had axillary node involvement.

The frequency of modified radical mastectomies decreased during the series, because of a change in philosophy in the management of breast carcinoma. Now, patients with focal areas of noninvasive cancer are treated by wedge resection only and closely followed up.

Discussion

We emphasize the use of dedicated equipment, proper compression technique and dedicated technologists and radiologists. To acquire expertise in this procedure, the radiologist should have follow-up data on all patients who have had breast biopsy recommended as a result of mammographic findings. This will increase diagnostic confidence and decrease mammographic overcall. In our view, it is necessary to have preoperative localization of the lesion verified by mammography. We see no virtue in inserting a needle preoperatively and not accurately localizing the lesion.[2] Even when performed by radiologists experienced in the procedure, needle localization on the first attempt may be inaccurate, requiring a reinsertion and further mammographic verification. Without this visual guidance the surgeon is operating "blind".

In their series, Schwartz and colleagues[3] reported a 31.4% incidence of carcinoma. The largest group had lesions 1 to 2 cm in diameter, which would not be considered minimal breast cancer. Fewer than six patients with infiltrating cancer in our series did not fulfil the criteria of minimal breast cancer in its broader definition. Schwartz and associates also reported a 37.8% incidence of axillary node involvement in patients with infiltrating cancer. Some of their patients had disseminated disease at the time of surgery but we could not document a single such case by conventional testing. The differences may be explained by different criteria of operability. Powell and colleagues[4] looked only at those patients with microcalcifications and noted a 17% incidence of carcinoma and a 9% incidence of axillary involvement.

All these reports confirm the simplicity of the procedure and the lack of serious morbidity, indicating that it is an effective tool in the armamentarium of the surgeon treating breast disease.

Conclusions

With the increased use of screening, suggestive changes found on mammography should be dealt with early and aggresssively owing to the substantial correlation with carcinoma. The term "aggressive" is not used to denote radical in the surgical sense, but early intervention as opposed to a "wait-and-see" attitude. Occult lesions can frequently be managed with conservative surgery.

It is time we discarded the notion that minimal breast carcinoma is not serious. In our series, almost 25% of clinically occult invasive breast cancers were associated with axillary involvement at the time of surgery. However, this represents a 50% decrease in axillary node involvement over carcinomas that present clinically and thus should result in improved survival.

Addendum

We have recently become concerned by the low cancer yield from mammographic lesions without calcification that have been described as either irregular nodular densities or asymmetric densities. Repeat mammography on the day of surgery has often failed to confirm a lesion and the proposed surgery has been cancelled. The discrepancy may be due to technical factors or regression of an area of benign breast disease. We now repeat the mammography before scheduling an operation. This policy, we believe, will reduce the number of unnecessary biopsies.

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Effect of Total Parenteral Nutrition on Biliary Lipids in Neonates

To study the effect of total parenteral nutrition (TPN) on biliary lipids in critically ill neonates, biliary lipid concentrations were determined in 13 neonates before starting TPN, in 8 receiving TPN for up to 2 weeks and in 9 receiving TPN for up to 8 weeks. Bile was very dilute in the 13 neonates not receiving TPN owing to a low concentration of bile acids. In many the bile-acid concentration was below the critical micellar concentration, thus cholesterol in bile was not dissolved. The neonates receiving TPN for up to 2 weeks showed a marked increase in bile-acid content and had levels above the critical micellar concentration. This apparently beneficial effect of TPN disappeared after 2 weeks and neonates who received TPN for 3 to 8 weeks again had bile-acid levels below the critical micellar concentration. Three conclusions may be drawn from this study: (a) in the fasting state before TPN is begun, the cholesterol content of bile relative to phospholipid and bile acids increased in linear fashion during the fasting period; (b) short-term TPN of up to 2 weeks' duration was associated with an increased bile-acid content to levels at which cholesterol could be dissolved; (c) neonates on long-term TPN and no oral intake secrete extremely dilute bile with an insufficient concentration of bile-acid molecules to form micelles to dissolve cholesterol. This finding may explain some of the adverse hepatobiliary changes associated with long-term administration of TPN.

Dans le but d'étudier les effets de l'alimentation parentérale complète (APC) sur les taux de lipides biliaires du nouveau-né gravement malade, les concentrations de lipides biliaires ont été mesurés chez 13 nouveau-nés sur le point de recevoir l'APC, chez 8 qui recevaient de l'APC depuis 2 semaines au maximum et chez 9 qui avaient été sous APC pour une période allant jusqu'à 8 semaines. La bile des 13 nouveau-nés qui n'avaient pas reçu d'APC était très diluée à cause de la faible concentration en acides biliaires. Chez plusieurs, la concentration d'acide biliaire était en deçà de la concentration micellaire critique de sorte que le cholestérol n'était pas dissous dans la bile. Les nouveau-nés qui avaient reçu de l'APC pour une période allant jusqu'à 2 semaines présentaient une augmentation marquée de la teneur en acide biliaire, au dessus de la concentration micellaire critique. Cet effet bénéfique apparent de l'APC avait disparu après 2 semaines et les nouveau-nés qui avaient été sous APC pour de 3 à 8 semaines avaient de nouveau des taux d'acides biliaires sous la concentration micellaire critique. De cette étude, trois conclusions peuvent être tirées: a) avant la mise en route de l'APC, la teneur en cholestérol de l'acide biliaire relative aux phospholipides et aux acides biliaires augmente de façon linéaire pendant la période de jeûne; b) à court terme (jusqu'à 2 semaines) l'APC est reliée à une augmentation des acides biliaires jusqu'à des concentrations permettant la dissolution du cholestérol; c) les nouveau-nés sous APC à long terme qui ne sont pas alimentés par la bouche sécrètent une bile extrêmement diluée dont la teneur en molécules d'acides biliaires est insuffisante pour former les micelles nécessaires pour dissoudre le cholestérol. Ces résultats sont capables d'expliquer quelques uns des changements hépatobiliaires indésirables qui sont reliés à l'APC à long terme.

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Disturbances of hepatobiliary function are common in patients of all ages receiving total parenteral nutrition (TPN) in place of normal oral alimentation.[1-3] Although TPN has been implicated by association as the cause of these conditions, it is difficult to separate the effects of TPN from those of prolonged fasting, underlying disease and, in neonates, liver immaturity. In neonates in an intensive care unit we studied biliary lipid (cholesterol, phospholipid and total bile acid) concentrations during the fasting state of up to 6 days before the start of TPN and for up to 8 weeks after.

Patients and Methods

Thirty neonates were divided into three groups. Group 1 (control) consisted of 13 babies who were fasting for up to 6 days before the initiation of TPN and were maintained on dextrose-electrolyte solution administered by peripheral vein. Group 2 comprised eight neonates on TPN for up to 2 weeks with no oral intake. In group 3 were nine patients who were on TPN for 3 to 8 weeks with no oral intake. Table I shows the incidence of neonatal jaundice and gastrointestinal disorders (predominantly necrotizing enterocolitis) affecting the enterohepatic circulation in the three groups. The incidence of neonatal jaundice in group 3 was less than in group 1 ($p < 0.05$), reflecting the older age of the neonates in the former group. The proportion of infants with gastrointestinal disorders did not differ significantly in the three groups. The groups were also similar in regard to gestational age, birth weight and weight at the time of study (Table I). Infants in group 3 tended to be heavier at the time of bile sampling, but the differences were not significant. None of the mothers had received phenobarbital before delivery.[4]

Total Parenteral Nutrition

The infants in groups 2 and 3 received TPN through a centrally-placed catheter. The amount of TPN was increased gradually and stabilized at a daily rate of 2.0 to 2.5 g/kg protein (Travasol; Travenol Canada Inc., Mississauga, Ont.), 2.0 to 3.0 g/kg fat (Intralipid; Cutter Laboratories, Mississauga, Ont.) and 12 to 15 g/kg glucose. Electrolytes, vitamins and trace elements were added to the TPN solution.

Collection and Analysis of Bile Specimens

Duodenal bile was obtained by duodenal intubation using a no. 5 to 8 French, soft rubber catheter passed with the patient positioned on the right side. The duodenal position of the tube was determined by pH monitoring (more than 6.5) and colour of the aspirate (yellow). Whenever possible tube position was verified by an x-ray film taken for other purposes (e.g., pneumothorax, pneumoperitoneum) or by palpation at the time of laparotomy. Gallbladder contraction was induced 20 minutes before we collected the bile specimen, by instilling an amino-acid solution (0.5 to 1.0 ml/kg of 10% Travasol) into the duodenum. Bile-rich duodenal juice was then aspirated over 1 to 2 hours to give a 1- to 3-ml specimen. Bile specimens were taken to the laboratory immediately after collection where they were extracted and refrigerated until they were analysed for lipid content.

The molar concentrations of cholesterol, phospholipid and total bile acids were determined for each specimen; from these data the total biliary lipid concentration was calculated. Cholesterol concentration was determined by an enzymatic colorimetric method using the Abbott bichromatic analyser — ABA-100 (Abbott Laboratories, South Pasadena, Calif.).[5] Phospholipid concentration was measured by the method of Sunderman and Sunderman[6] using the Unicam spectrophotometer (Pye Unicam Ltd., Cambridge, UK) at 675 nm. The enzymatic determination of total bile acids was carried out using the method of Engert and Turner[7] and the Beckman DU-8 spectrophotometer (Beckman Instruments, Fullerton, Calif.) at 340 nm.

We attempted to portray the biliary lipid data on triangular coordinates and to use Carey's tables[8] for cholesterol solubility in bile; however, the extremely dilute nature of bile in the premature neonate puts most specimens out of the range of these devices. The data are presented as a percentage of total lipid millimoles and total lipid concentration with reference to cholesterol solubility in bile in only group 1. Tests of statistical significance (Student's *t*-test for unpaired data, χ_2 test and linear regression analysis) were done using a Hewlett-Packard 97 programmable calculator (Hewlett-Packard [Canada] Ltd., Mississauga, Ont.).

The study was approved by a University of Alberta, Faculty of Medicine, Ethical Review Committee. Parental consent was obtained after a full explanation of the study as was the consent of a neonatalogist who was not involved in the study.

Results

The concentration of lipids in the bile of neonates studied was extremely dilute compared with the generally stated range for normal adults (Fig. 1, Table II). Dilute bile was noted in all three groups but particularly in groups 1 and 3. The total biliary lipid concentrations of only three specimens, all from group 2, fell within the lower limits of the normal adult range.[8]

When total biliary lipid concentration is broken down into the three components (cholesterol, phospholipid and total bile acids), it is apparent that cholesterol and phospholipid concentrations in bile changed little in the three groups (Table II). Total bile-acid concentration showed a large increase in group 2 compared with groups 1 and 3 and accounts for the increase in total biliary lipid concentrations seen in that group (Fig. 2, Table II).

The critical micellar concentration (CMC) or minimum concentration at which micelles start to form for bile acids in bile is 0.9 to 2.2 mmol (mean 1.45 mmol).[9,10] Five of the 13 neonates in group 1 showed bile-acid concentrations below the CMC. In group 2 in which bile-acid concentration was much higher, all bile specimens were at or above the CMC. In group 3 the concentrations of only two specimens were at the lower range of the CMC for bile acids and in the remaining seven, specimens were clearly below the CMC (Fig. 3).

In group 1 patients (control group), the relation between cholesterol in bile expressed as a percent of total lipid mil-

Table I—Infant Data

Feature	Group 1 (n = 13)	Group 2 (n = 8)	Group 3 (n = 9)
Male/female	8/5	4/4	4/5
Duration of total parenteral nutrition, wk	0	2	3–8
Neonatal jaundice, no.*	10	5	3
Gastrointestinal disorder, no.	8	7	8
Gestational age, wk (x ± SEM)	33.3 ± 1.2	33.8 ± 1.6	32.8 ± 1.8
Birth weight, g (x ± SEM)	1892 ± 201	1784 ± 213	1858 ± 297
Weight at time of testing, g (x ± SEM)	1938 ± 192	2070 ± 223	2651 ± 357

*Group 1 vs group 3 $p < 0.05$.

Table II—Lipid Concentrations for the Three Groups of Neonates*

Lipid values	Group 1	Group 2	Group 3
Total bile, g/L	1.17 ± 0.19	2.49 ± 0.49	0.77 ± 0.10
Cholesterol, mmol/L	0.30 ± 0.05	0.40 ± 0.05	0.23 ± 0.04
Phospholipid, mmol/L	0.70 ± 0.16	0.67 ± 0.10	0.56 ± 0.08
Total bile acids, mmol/L	1.04 ± 0.18	3.67 ± 0.88	0.50 ± 0.12

*Normal adult range of total biliary lipid concentration is 3 to 300 g/L.

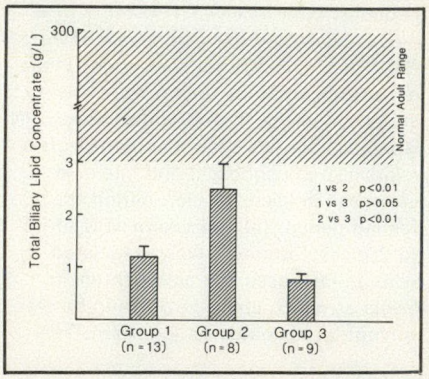

FIG. 1—Total biliary lipid concentration (g/L) in groups 1, 2 and 3 (mean ± SEM). Shaded area indicates normal range for total biliary lipid concentration.

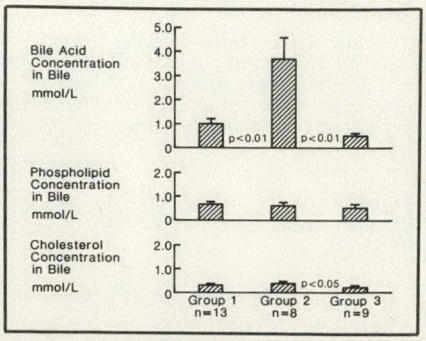

FIG. 2—Concentrations of cholesterol, phospholipid and bile acids (mmol/L) in bile (mean ± SEM).

limoles and duration of the fasting period in days was linear ($y = -18.72 + 7.37x$) with a correlation coefficient of 0.90 (Fig. 4). This temporal relation did not apply in groups 2 and 3 and or to phospholipid or bile acids in any group. This relation between biliary cholesterol and fasting is also seen in normal adults in whom bile tends to become supersaturated with cholesterol during fasting. In Fig. 4 we have indicated the cholesterol solubility line of Admirand and Small[11] (at approximately 10% cholesterol-percent of total millimoles) as a reference point.

Discussion

A notable finding in this study was that the infants in groups 1 and 3 had extremely dilute bile compared with that of adults[8] and full-term infants.[4] This was owing mainly to the small amount of bile acid present in the bile obtained from the duodenum. This observation is consistent with the finding that the functional maturity of the liver is reduced in premature infants, whose livers cannot carry out the complex functions of synthesizing bile acid from cholesterol, conjugating the bile acid with glycine or taurine and secreting the conjugates into bile. The most important finding was that bile became more concentrated in the neonates in group 2 who received TPN for up to 2 weeks due to a large increase in bile-acid content. Short-term TPN appeared to provide substrate for bile-acid synthesis or in some way "turned on a switch" for bile-acid conjugation and secretion. Unfortunately this beneficial effect was short lived as infants receiving TPN for longer than 3 weeks again had very dilute bile. It is noteworthy that Postuma and Trevenen[12] and Cohen and Olsen[13] noted a deterioration in liver function and histologic changes in the livers of neonates receiving TPN for longer than 14 days.

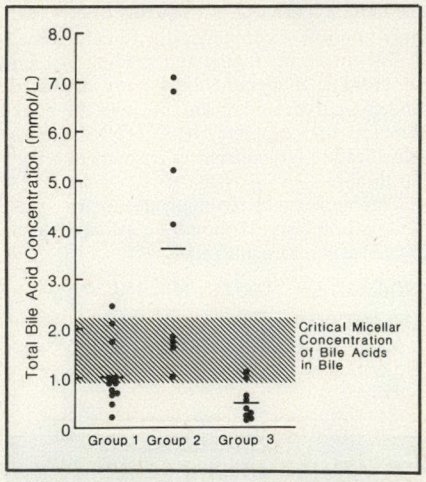

FIG. 3—Total bile-acid concentrations (mmol/L). Shaded area indicates critical micellar concentration of bile acids in bile.

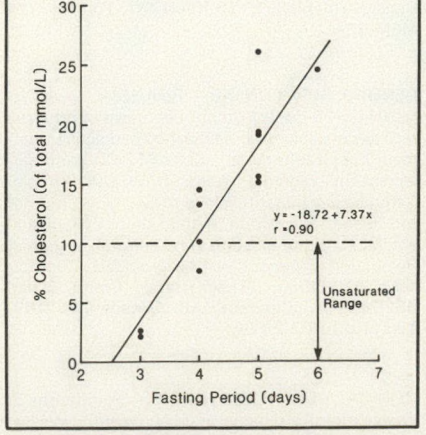

FIG. 4—Percent cholesterol in bile plotted against duration of fasting period for group 1 (control group receiving no TPN). Broken horizontal line indicates approximate limit of cholesterol solubility in bile.

A consequence of the dilute bile and low bile-acid content seen in groups 1 and 3 infants is that their bile-acid level was below the critical micellar concentration for bile acids; this is the level below which there are insufficient bile-acid molecules present to form micelles to dissolve cholesterol. Although the bile sludge and stones formed in the gallbladders of patients on TPN has largely been attributed to gallbladder stasis,[14,15] the bile of many infants in this study was also incapable of solubilizing cholesterol.

The neonates in group 1 (fasting without TPN) showed the same type of relation between cholesterol content of bile (as a percent of total millimoles) and fasting as is seen in normal adults; namely, that bile becomes supersaturated with cholesterol in the fasting state.[16–18] The bile content of cholesterol relative to bile acids and phospholipids increased during the fasting period of up to 6 days. In Fig. 4 we have indicated the cholesterol solubility line of Admirand and Small as a reference point only because some bile samples in this group were below the critical micellar concentration for bile acids and were incapable of solubilizing even relatively small amounts of cholesterol.

In summary, it appears that bile becomes increasingly saturated with cholesterol in fasting neonates. However, short-term TPN (up to 2 weeks) is associated with an increase in bile-acid content and hence decreased cholesterol saturation of bile. These effects disappear on continued TPN without oral intake. The reasons for the apparent beneficial effect of short-term TPN need further investigation.

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Index Reminder

The 1983 index to the *Canadian Journal of Surgery,* volume 26, is still available. If you would like to receive a copy, please return the request card that was included in the November 1985 issue or notify the Library, *Canadian Journal of Surgery,* PO Box 8650, Ottawa, ON K1G 0G8; (613) 731-9331.

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microbiologists, hospital administrators and chiefs of service, and should probably be required reading. The busy clinical surgeon and surgical resident are more concerned with the 30% to 40% of surgical patients who are admitted with home-based spontaneous infection from acute inflammation or viscus perforation, the proper choice and use of antibiotics (both prophylactic and therapeutic) and surgical techniques. They will be more attracted to the chapters concerning influence of operating technique on rate of wound infection; inhospital (nosocomial) infections other than surgical wound infection; use of antimicrobial agents and infection in the immunocompromised host.

The chapter on operating technique is disappointingly elementary and dated. The principles enunciated—careful technique to minimize tissue injury, protection of wound edges, débridement of dead tissue, hemostasis and avoidance of seroma and dead space—are basic. Of the 20 references, 13 are earlier than 1971 and only 2 are from reports of the 1980s. Equally disappointing is the chapter on pathophysiology of infection that reviews the inflammatory and immunologic responses of the invaded body and the energy metabolism and synthesis of proteins essential to maintain immunocompetence, to heal wounds, and to preserve the structure of vital organs. Although it introduces the average practitioner to a dazzling array of new terms (e.g., leukocidin, bacterial L-forms, erythrogenic toxin, lipid A, kallikrein, opsonic proteins, peptidases, thromboxane, prostacyclin, interleukin and fibronectin), this kaleidoscopic review is overwhelming. In attempting to touch all bases, it fails to develop a comprehensive picture. This is probably more a reflection of the state of the art than a failure of the editors. The defects in these two chapters are compensated for by the outstanding in-depth tabulated review of the classes of antimicrobial agents, their mode of action and side effects, and a guide to the selection of the most appropriate agent or an alternative. This is complemented by an excellent review of the causes and prevention of nosocomial infection, especially of the catheterized urinary tract, and the diagnostic and special preventive and therapeutic considerations in infections in immunodepressed patients (the aged, malnourished and critically ill) that are being encountered with increasing frequency. These two chapters alone make this a worthwhile reference text.

It is noteworthy that there has been a shift of the bacteria in secondary infections occurring during hospitalization (hospital acquired or nosocomial) from gram-positive *Staphylococcus*, the major offender, to predominantly aerobic gram-negative bacilli. There has also been a sharp increase in the number of infections caused by invasive gram-negative bacteria previously considered to have little or no virulence, and infections by fungi and viruses. Approximately 80% of serious infections by these organisms developed while patients were on antibiotic prophylaxis or therapy for other infections. It is incumbent upon the operating surgeon to be familiar with their control.

The organization, headings, layout and print make this manual easy to read and subjects easy to locate. There is liberal use of drawings and photographs, most of which add little to the text and are redundant but serve well to break the monotony of the written page. The multiple tables and lists are exhaustive but useful.

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TUMORS OF THE KIDNEY AND URINARY TRACT. Color Atlas and Textbook. Steen Olsen. 291 pp. Illust. Munksgaard International Publishers Ltd., Copenhagen, 1984. Price not stated. ISBN 87-16-09040-3.

When many urology texts seem to be word-processor-generated variations of each other, it is refreshing to read this book.

Urologists and pathologists will find the book both enjoyable and beneficial. Its emphasis is on histologic features and ultrastructure. The full colour micrographs are of the highest quality and clearly illustrate the text. They are particularly good in the controversial sections such as those on urothelial atypia, renal cell adenoma and carcinoma.

The book begins with a clear and logical discussion of the problems of definition and terminology of renal cell adenoma and carcinoma. The author does not draw a definite line between adenoma and carcinoma, but he narrows the grey area and highlights the dilemma facing the histopathologist trying to distinguish between the two.

Lesions mistaken for tumours, such as cystitis cystica and malakoplakia, are discussed, and the diagnostic features are well illustrated; prostatic hyperplasia is discussed briefly and only to allow a comparison with carcinoma.

The different staging and grading systems of urologic malignant disease are discussed and compared, and as an appendix the book contains the complete UICC (TNM system) classification. The references are numerous and up to date.

This book can be recommended to urologists and pathologists. It should be available as a reference in all teaching units.

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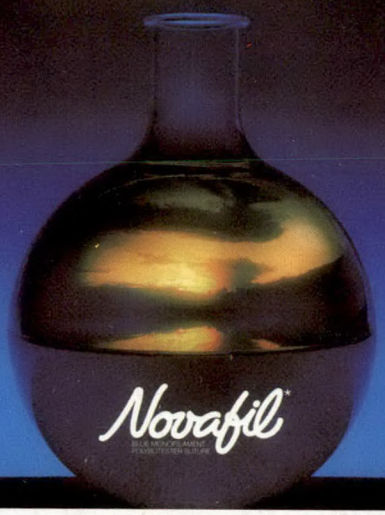

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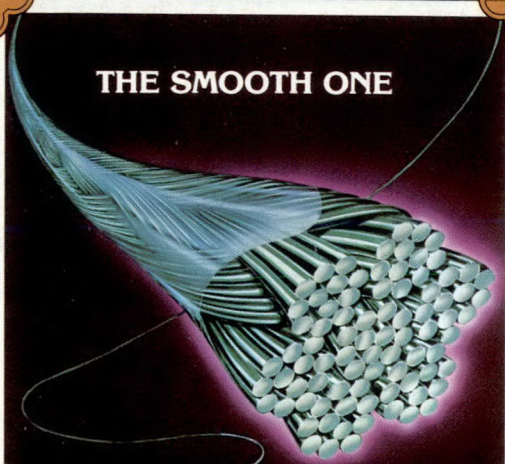

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