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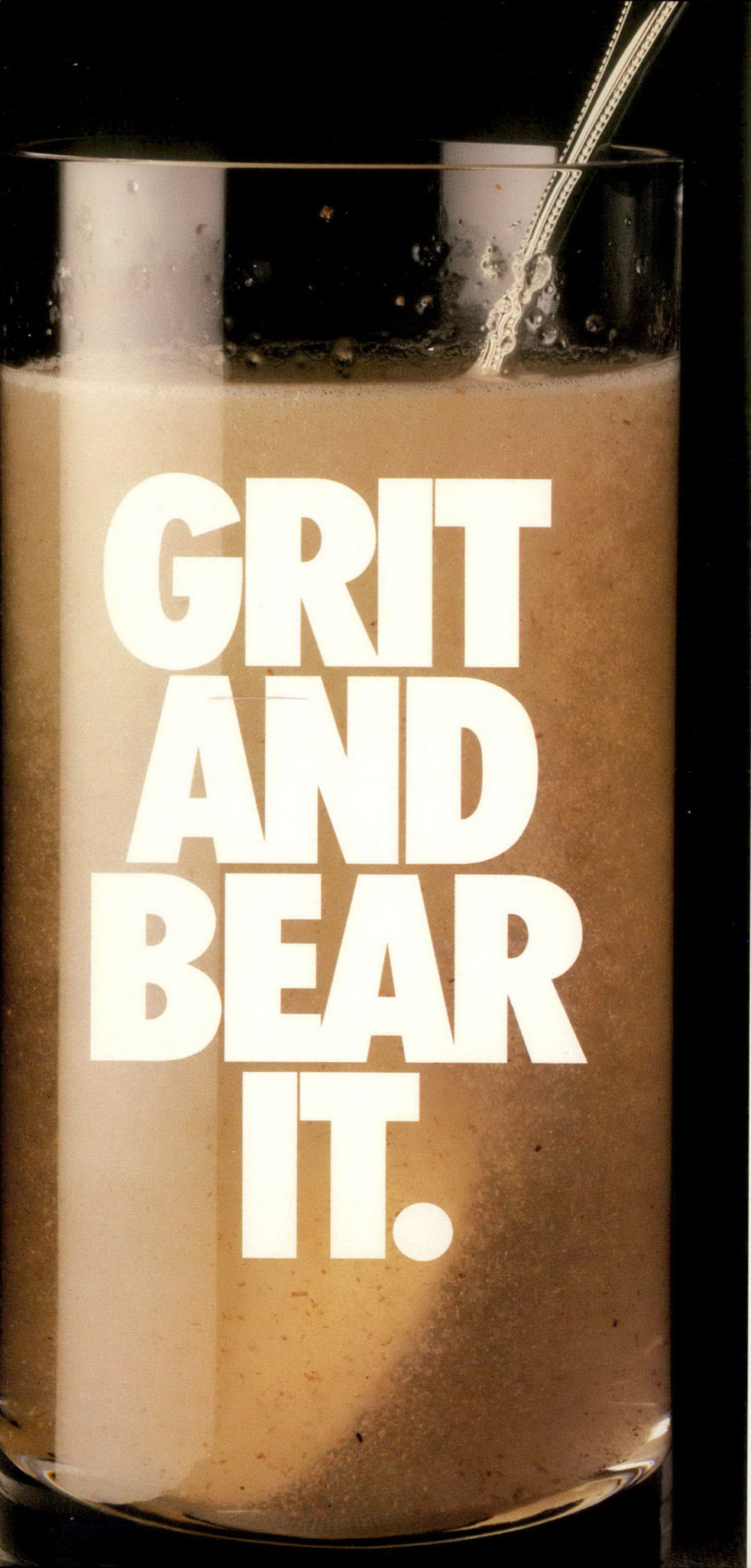

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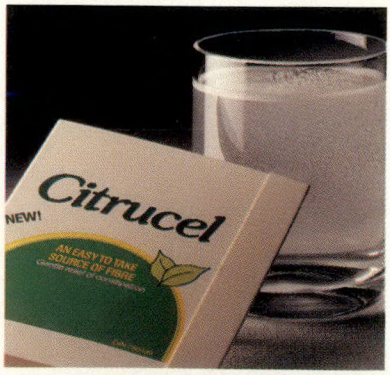

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HISTORY OF SURGERY

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.

Defunctioning Colostomy: an Outmoded Operation?

For many years primary resection with anastomosis has been the treatment of choice for lesions causing total obstruction of the right colon. It has the attraction of removing the lesion, anastomosing to collapsed, albeit unprepared, colon using small intestine that can be decompressed by milking the liquid contents back or into the portion of bowel to be resected.

In marked contrast, surgeons have been much less inclined to resect such lesions in the left colon and to perform primary anastomosis.

We were all influenced by the low mortality (8%)[1] reported as early as the 1940s when right transverse colostomy was performed for obstructing left colonic lesions; previously, when cecostomy had been used, the death rate for large-bowel obstruction was 50%.[2] After a totally diverting colostomy and before definitive resection it is possible to cleanse the colon completely so that a wider resection can be performed if carcinoma is the cause of obstruction.

In our teaching, we have always emphasized the hazardous nature of large-bowel obstruction, which can be a "closed loop" type with urgent need for decompression. Modern textbooks suggest right transverse colostomy[3] as the initial treatment for obstructing lesions of the left colon, but if resection is preferred primary anastomosis is not recommended.[4,5] A one-stage procedure with primary anastomosis has been proposed but with total abdominal colectomy and ileorectal anastomosis in order to avoid using distended colon in the anastomosis.[5–7]

A randomized prospective trial comparing resection and immediate anastomosis with traditional management in two or three stages has not been done for obstructing lesions of the left colon.

In this issue of the Journal (pages 167 and 168), Goodall and Park, in a remarkable report on 40 patients with totally obstructing left colonic lesions, advise immediate resection with colocolostomy. During the period of the study, 1981 to 1986, 20 other patients with total obstruction were treated at their hospital, by either the Hartmann procedure or anastomosis with protective colostomy. Of the study group of 40 patients, 30 had carcinoma, 9 diverticulitis and 1 volvulus as the cause for the obstruction. In three patients perforations had occurred and in two an intraperitoneal abscess existed at the time of surgery.

Two patients died — one, aged 84 years, of myocardial infarction, the other, aged 89 years, of pneumonia — a death rate of 5%. Morbidity was acceptable and could probably have been diminished even further, as the authors state, by using delayed primary wound closure.

This is not a randomized trial and the authors do not tell us the fate of

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Detailed instructions to contributors, in English and French, appear on page 69 of the January 1988 issue.

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

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the 20 patients with left colonic obstruction treated differently during this same period. The results could not have been much better. It is gratifying to see these impressive results, especially in the elderly who can be overwhelmed by the necessities of care of a colostomy.

In patients with cancer as the cause of obstruction some might prefer a two- or three-stage operation in order to obtain a wider resection and possibly a better long-term survival. However, obstructing cancers are usually more advanced lesions. A prospective trial supporting the concept that a wider resection on prepared bowel increases survival rate in this setting has also not been done. One retrospective study of primary versus staged resection for obstructing left colonic cancers reported 5-year survival rates of 63% and 33% respectively.[8] These differences are significant but may indicate that the more favourable lesions with a better prognosis were treated by primary resection.

In the report by Goodall and Park the colonic anastomosis is protected by aspirating the contents of the colon at surgery and packing the proximal opening with Gelfoam to prevent fecal material from coming into contact with the anastomosis during the initial phases of healing. In another study,[9] an intracolonic device, Coloshield (Deknatel, Lake Success, NY) has been used for the same purpose in 28 patients with diverticulitis and perforation who underwent one-stage colectomy and colocolostomy. Of these 28 patients, 18 had paracolic abscesses and 10 generalized peritonitis at the time of surgery. There were no anastomotic leaks and no deaths.

Should a transverse colostomy be used to protect a left-sided anastomosis? There may be some argument for this if the resection is elective, bowel preparation was possible and the anastomosis is technically difficult. It is not rational to do a protective colostomy after emergency resection and anastomosis when the large bowel proximal to the anastomosis and distal to the colostomy is heavily contaminated and likely to cause major peritonitis if there is a disruption of the anastomosis. Local drainage and colostomy for perforated diverticulitis are known to be associated with a high death rate (10% to 48%).[10,11]

We must conclude that defunctioning colostomy without resection is now rarely indicated even in totally obstructing and perforated left colonic lesions.

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Colonoscopy After Resection for Bowel Cancer — Is It Already Too Late to Answer the Questions?

At the time of primary resection of a colorectal carcinoma, the entire colon should be examined carefully, even in areas remote from the primary tumour, and all coexisting polyps and synchronous cancers should be removed. At follow-up, the colon should be routinely examined to treat metachronous cancers at an early stage and to remove all polyps when they are small, before cancer develops. This should benefit the patient by reducing the occurrence of second cancers and the overall death rate. There are a large number of "shoulds" in the foregoing statements and the paper in this issue of the Journal by Vasilevsky and Gordon, entitled "Colonoscopy in the follow-up of patients with colorectal carcinoma" (pages 188 to 190), helps us to examine at least one of these critically.

There appears to be increasing acceptance by general surgeons of the case management method described above. It is an attractive concept that the entire colon can be completely "cleaned" of benign and malignant masses at the time of primary resection of a carcinoma and subsequently kept "clean" by repeated colonoscopy, with obvious patient benefit. There is no question that the more often and the more rigorously the colon is examined, the more lesions will be discovered and diagnosed than

would otherwise be possible, or that the majority of these small lesions can be removed endoscopically. The unanswered questions concern which regimen of surveillance should be followed, which methods of colonic examination should be used and to what extent these programs benefit the patients. As in so many areas of modern medicine, the acceptance of regular follow-up protocols has occurred far ahead of the evidence for their benefits. Even when the answers to these questions are clear, we still must answer the last (and most difficult) question in coming to a management decision — that is, do the benefits outweigh the costs?

Our understanding of the natural history of colorectal polyps and their relationship to carcinoma is at present inadequate to permit a definite recommendation on the desirable frequency of follow-up after primary resection of colorectal cancer. The contribution by Vasilevsky and Gordon does help us to assess the relative benefits of colonoscopy as opposed to radiology. All of their patients had normal barium enema findings and the subsequent findings at colonoscopy would, presumably, have been missed until at least the time of the next follow-up examination. In summary, they found 2 anastomostic recurrences, 2 metachronous cancers and 22 neoplastic polyps (of which 10 were greater than 1 cm in size) in their 100 patients. The study design is open to the criticism that only single-contrast barium enema examination was performed, and their statement that this is the examination most commonly performed (rather than double-contrast barium enema) is no longer true for most major centres.

A pros and cons list may be drawn up for colonoscopy versus barium enema examination in postoperative surveillance of the colorectum. Neither method is an enjoyable experience for the patient, but the compliance with suggested follow-up programs is high. Complete colonoscopy, a procedure described as "difficult" in 25% of cases by highly experienced colonoscopists,[1] was achieved in 94% of the patients in the current series. Barium enema study achieves about the same level of completeness overall.[2] Colonoscopy and double-contrast barium enema have about the same rate of false-negative results (about 10%), but colonoscopy has no false-positive results.[3] Colonoscopy can certainly detect lesions smaller than can be seen on double-contrast barium enema examination, but, as the authors discuss in detail, the clinical importance of small polyps is a major question. Perforation is rare and bleeding uncommon after colonoscopy and even more so after barium enema. A major advantage of colonoscopy is its operative capability. If one must choose between the two techniques, colonoscopy seems to have the edge. Why not use colonoscopy and double-contrast barium enema together? This would raise the sensitivity to near 100%.[4] This question can only be answered in relation to the overall benefit–cost equation, which is the key issue.

Cost–benefit analysis of an intervention is always difficult, because different people will always take the same data and come to totally different conclusions based on different values. There is no doubt that too few cancers are found on follow-up by colonoscopy to justify the costs and hazards of the intervention, but what about the polyps? A rate of 25 polyps in 100 patients would seem adequate to justify the procedure, but this is where we have the final missing link in the chain. The evidence that colorectal polyps are associated with colorectal cancer is strong,[5] but more evidence is desperately required on the actual clinical benefit that may be expected by removing them prophylactically. Unfortunately, the answer to this question has been pre-empted by many surgeons and gastroenterologists who have adopted protocols that have been advocated prematurely. Not only is this question suitable for a randomized prospective trial, but the large number of patients that could be collected in a comparative study in a relatively short time would ensure a valuable answer. There is an ideal opportunity here for a collaborative research protocol to be organized by a Canadian general surgical organization such as the Canadian Association of General Surgeons or the Canadian Association of Clinical Surgeons. The question is circumscribed, important and answerable. The protocol would require randomization of patients after primary resection into two groups, one managed on the basis of subsequent signs and symptoms and the other managed by regular colonoscopy in addition. Unfortunately, it may already be too late for surgeons and gastroenterologists to comply with such a study because of entrenched clinical behaviour. Compliance can be expected only if we acknowledge that we do not know the answer to the question.

Large fees are generated by endoscopy and there is a medical-political minefield here in terms of appropriate and possible contraction of indications for the procedures. Health economists and government agencies should recognize the need for research funding on issues like this, and physicians should recognize the need for adequate evaluation of protocols before mass implementation — there we have another couple of "shoulds" to add to the list. Without proper evaluation we cannot even begin to address the benefit versus cost issue; we don't even know whether we are causing net harm to our patients regardless of the dollars and resources aspects of cost.

We desperately need to know the answer to these questions: does annual colonoscopic follow-up of patients after primary resection of colorectal cancer reduce mortality; if so, by how much? It simply will not do to claim that the answer is obvious because polyps can be detected and removed at colonoscopy. Any suggested protocol for unpleasant, costly and potentially dangerous intervention such as colonoscopy requires validation. We often lament the progressive reduction in bench surgical research, but here is an example of the prime importance of evaluative research for which the majority of surgeons are most suited. To acknowledge ignorance, however, is a prerequisite to seeking the required knowledge. Let us not dig the trenches around clinical behaviour so deep that it becomes completely impossible to evaluate it. Let us not pretend that the answers to the questions are so obvious that even asking them is inappropriate.

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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.

Royal College Statement on Informed Consent

Complying with legal requirements for obtaining a patient's consent before medical treatment does not ensure that acceptable ethical standards have been met, advises the Biomedical Ethics Committee of the Royal College of Physicians and Surgeons of Canada, since "higher standards of informed consent than those required by law may be appropriate". In a recently released statement by the Royal College, the principles of informed consent are discussed, guidelines for procedures for obtaining a patient's consent provided and a set of maxims outlined.

Because in our society so much value is placed on the rights of the individual, to entrust the physician with absolute authority would not be acceptable. Therefore, patients have the right to make decisions concerning their medical care after receiving sufficient information from their physician. This, of course, applies only to patients who are able to take the responsibility and who wish to do so. The Committee recommends procedures to follow in other instances: a competent patient cannot make a decision or leaves it to the physician to make a decision; a patient is incompetent (e.g., an infant, unconscious or severely retarded); a patient is incompetent and it is an emergency situation; a patient's competence is uncertain.

Copies of the statement are available from the Communications Section of the Royal College of Physicians and Surgeons of Canada in Ottawa.

Task Force Formed to Analyse Use of Health Care Services in Ontario

Ontario Health Minister Elinor Caplan and Ontario Medical Association (OMA) President Hugh Scully announced recently that the Ministry of Health and the OMA have formed a task force to study the use of medical services in the province.

The task force has been formed to look for answers to a worrying problem — the rising cost of health care in Ontario. Said Health Minister Caplan, "I have been concerned about the demands on our health care system and the use of medical services since I took over this portfolio."

One of the task force's goals is to identify the factors that influence both how the health care system is used and how demand on resources is created, such as increasing requests for services from patients, physician behaviour, or the use of more sophisticated diagnostic and treatment methods.

When these influencing factors have been identified and documented, the second goal of the task force can be achieved — to formulate a series of recommendations that will reinforce "sound practices" and "modify any behaviour that has resulted in inappropriate use of the health care system in Ontario".

The task force intends to achieve its goals by the following means:

- Gathering and analysing data provided by the Ministry, the OMA and other sources, including research literature.
- Using this information to identify the factors that influence the use of health resources, such as: physician services in offices, hospitals and other settings, technology, changing demographics, legislation and the political process, changing malpractice climate and growing public education and awareness.
- Initiating studies to determine what resources and structures are necessary to provide optimal health care.
- Developing short- and long-term plans designed to achieve efficient use of medical services without compromising their quality.

The chairman of the nine-member task force is former Deputy Minister of Health Graham Scott. Quarterly reports will be submitted to the Ministry of Health and to the OMA, and there will be an annual review of the task force's progress by the two bodies.

Princess Margaret Hospital's New Radiotherapy Unit Approved

Toronto's Princess Margaret Hospital, the largest cancer treatment, research and teaching centre in Canada, has received approval from Ontario's Ministry of Health to proceed with plans for a new radiotherapy unit to be housed in the basement of Mount Sinai Hospital. Construction of the unit will begin in April 1989 and is the first step in the reconstruction of the Princess Margaret Hospital, which by 1995 should be situated at its new location adjacent to Mount Sinai Hospital on University Avenue. There will be 16 radiotherapy machines operating at the new hospital, including the 4 in the Mount Sinai unit. The Princess Margaret Hospital currently operates nine radiotherapy machines.

LAUREL WILLIAMSON

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

A section on surgical technique, supervised by Dr. N.M. Sheiner

PHILIP H. GORDON, MD, FRCSC, FACS

Ivalon Sponge Wrap Operation

Numerous operations have been described for the many distressing symptoms of rectal procidentia. In the good-risk patient, the Ivalon (supplied by Downs Surgical Canada Ltd., Cooksville, Ont.) wrap operation described by Wells[1] has been effective. There are several variations of this operation[2-6] and the technique I have found satisfactory is as follows.

Technique

With the patient in the supine position the bladder is catheterized and the skin prepared with a suitable antiseptic. The abdomen is entered through an infraumbilical transverse incision. The table is tilted to the Trendelenburg position to facilitate packing the abdominal viscera into the upper abdomen. Taking care to protect the ureters, the surgeon incises the peritoneum on each side of the rectosigmoid, beginning about 5 cm above the pelvic brim (Fig. 1). The presacral space is entered at the level of the sacral promontory and the rectum is gently and fully mobilized from the sacral hollow to the level of the coccyx (Fig. 2), avoiding the presacral nerves (Fig. 3). To permit anterior mobilization, the lateral peritoneal incisions are extended distally to join each other in the deepest portion of the cul-du-sac (Fig. 4). With the rectum grasped in the left hand, a plane of dissection is achieved with the fingers of the right hand. Dissection in this plane need not be extensive as a deep cul-de-sac is a characteristic of most cases of complete rectal procidentia, and the seminal vesicles or vaginal vault is easily reached. The lateral stalks, or at least their upper portion on each side, are divided between clamps and ligated with an absorbable suture. If the rectum is not fully mobilized, redundant rectum below the point of fixation may cause the prolapse to recur. Throughout the procedure, meticulous hemostasis is essential since hematoma formation may predispose to infection of the sponge.

A rectangular sheet of previously sterilized Ivalon is then moistened in normal saline to make it pliable. Three sutures of a material such as 2-0 Prolene or 2-0 Vicryl on a noncutting needle are then passed through the Ivalon sponge, the presacral fascia and then back through the Ivalon sponge (Fig. 5). The distal suture should be placed as low as possible, deep in the pelvis. The sponge is then "railroaded" into the pelvis and the sutures are tied (Fig. 6).

The mobilized rectum is drawn upward and placed in front of the Ivalon sheet, the lateral ends of which are folded to encompass approximately three-quarters of the circumference of the rectum. The residual gap is essential to prevent constriction of the lumen. Excess Ivalon is excised and a series of three 3-0 Prolene or 3-0

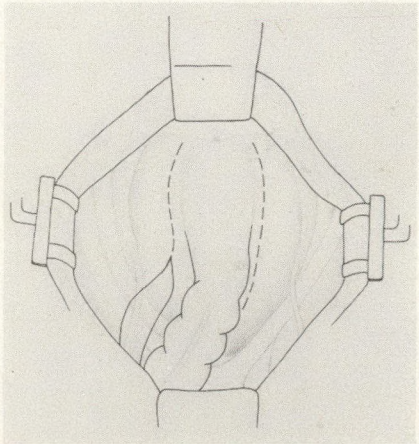

FIG. 1 — Peritoneum incised on both sides of rectosigmoid, beginning 5 cm above pelvic brim.

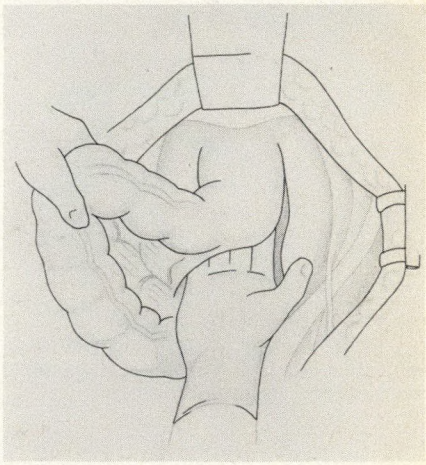

Fig. 2a

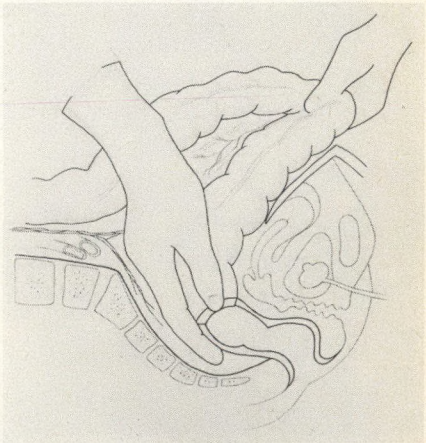

Fig. 2b

FIG. 2 — (a) Mobilization of rectum accomplished by gentle manual dissection, avoiding presacral plexus of veins. (b) Sagittal view. Dissection carried down toward tip of coccyx, preserving mesorectum.

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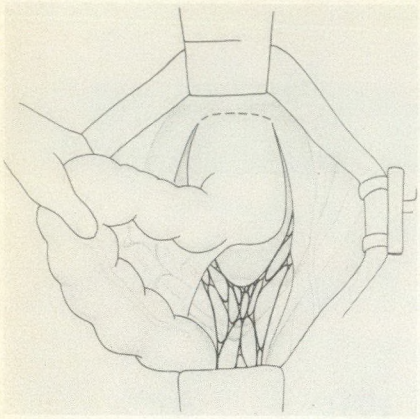

FIG. 3 — Lateral incisions joined in anterior cul-de-sac. Presacral neural plexus should be left intact.

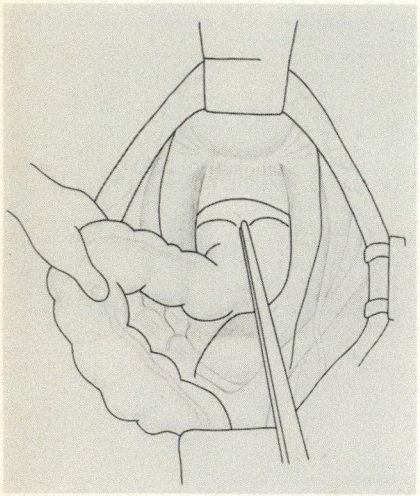

FIG. 4 — Blunt or sharp dissection frees anterior rectal wall. Peritoneum of anterior cul-de-sac is retracted superiorly.

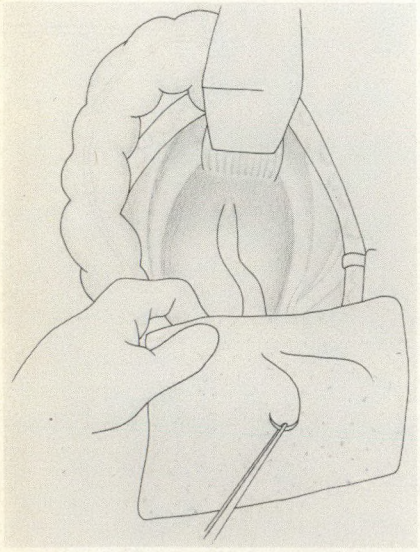

FIG. 5 — Sheet of Ivalon sponge sewn to presacral fascia with interrupted 2-0 polypropylene suture material on round needle. Rectum is retracted forward away from sacrum.

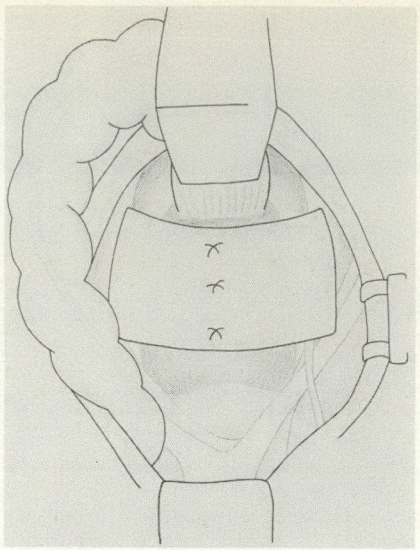

FIG. 6 — Three polypropylene sutures hold Ivalon immobile against presacral fascia.

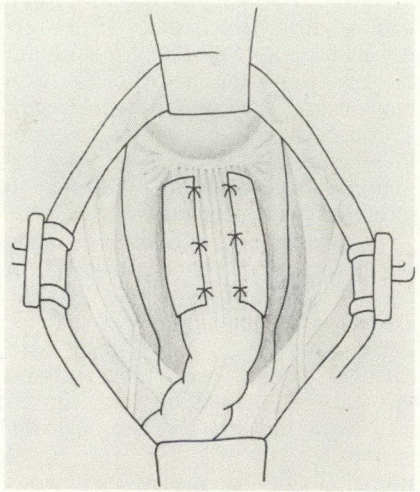

FIG. 7 — Ivalon sheet applied to posterior three-quarters of circumference of rectum and sutured in place with 3-0 polypropylene sutures on each side.

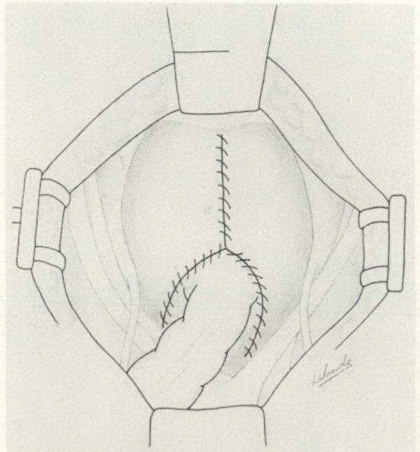

FIG. 8 — Operation completed by closing pelvic peritoneum.

Vicryl sutures is used on each side to fasten the lateral limbs of the sponge to the anterior aspect of the rectum (Fig. 7).

The sponge is extraperitonealized by closing the pelvic peritoneum with continuous 3-0 chromic catgut (Fig. 8). No drains are used. Postoperatively, fluids are given intravenously until ileus has resolved. Nasogastric suction is usually not necessary. The Foley catheter is removed on day 2. It is essential to ensure that the patient does not strain at defecation, so as soon as oral feeding is tolerated, a bulking agent in the form of a psyllium seed preparation is given, supplemented by Milk of Magnesia as necessary.

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Cyclosporin A Metabolites Suppress T-Cell Proliferation by Concanavalin A and in a Mixed Lymphocyte Reaction

To ascertain if cyclosporine metabolites (CMs) have immunosuppressive activity, bile, whole blood and urine taken from patients after cholecystectomy and from a liver transplant recipient on cyclosporin A (CsA) were assayed to determine their effect on T-cell proliferation induced by concanavalin A (Con A) and in a two-way mixed-lymphocyte response. Bile and whole blood from the liver transplant patient completely suppressed Con A proliferation and the mixed lymphocyte response (MLR) at dilutions at which normal bile and whole blood have no suppressive activity, but no such activity was noted from the urine. The CMs were separated into six peaks (fractions) by high-pressure liquid chromatography (HPLC). Metabolites were identified by internal standards and HPLC/mass spectrophometric analysis. Cyclosporine metabolite fractions 2 and 3 from bile and blood had immunosuppressive activity similar to parent CsA whereas fractions 5 and 6 demonstrated less but substantial immunosuppressive activity. Fractions 2, 3 and 5 demonstrated an ability to inhibit two-way MLR similar to parent CsA; the other metabolite fractions were able to inhibit the MLR but to a lesser extent.

These results demonstrate that a number of CMs have immunosuppressive effects similar to those of the parent compound, and this may account for the lack of correlation between whole blood CsA levels and immunosuppressive activity.

Afin d'établir si les métabolites de la cyclosporine possèdent une activité immunosuppressive, la bile, le sang entier et l'urine de patients qui eurent à subir une cholécystectomie et ceux d'un greffé du foie traité à la cyclosporine A ont été dosés d'après leurs effets sur la prolifération des lymphocytes T provoquée par la conacavaline A et sur la réponse bi-directionnelle de lymphocytes en culture mixte. La bile et le sang entier du greffé du foie ont complètement supprimé la prolifération provoquée par la conacavaline A et la réponse des lymphocytes en culture mixte à des dilutions auxquelles la bile et le sang entier normaux n'exercent aucune activité immunosuppressive; toutefois, aucune activité n'a été décelée dans l'urine. Les métabolites de la cyclosporine ont été séparés d'après six pics d'élution (fractions) par chromatographie liquide à haute performance (HPLC). Les métabolites ont été identifiés à l'aide de standards internes et par HPLC/spectrophotométrie de masse. Les fractions 2 et 3 de la bile et du sang possédaient une activité immunosuppressive semblable à celle du produit père, alors que les fractions 5 et 6 démontraient une activité moindre mais quand même importante. Les fractions 2, 3 et 5 montraient une activité semblable à celle de la cyclosporine A contre la réponse bi-directionelle des lymphocytes en culture mixte. Les autres fractions métaboliques étaient capables d'inhiber la réponse des lymphocytes en culture mixte mais à un degré moindre.

Ces résultats démontrent que certains des métabolites de la cyclosporine possèdent des effets immunosuppresseurs semblables à ceux du produit père et ceci peut expliquer le peu de corrélation observé entre les taux de cyclosporine A dans le sang entier et l'activité immunosuppressive.

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Cyclosporin A (CsA) is a biologically active product of the fungus *Trichoderma polysporum*.[1] It is a chemically neutral, extremely hydrophobic, cyclic polypeptide composed of 11 amino acids.[2] Previous studies using tritiated CsA demonstrated that the molecule is rapidly and extensively metabolized mainly through the monooxygenase cytochrome P450 system in man and that the liver is the major site of its elimination.[3,4] Over 50% of an intravenously administered dose of CsA is excreted in bile, predominantly in metabolite form, and less than 0.1% is excreted as parent CsA.[5] In contrast, less than 6% of the administered dose excreted in the urine contains more than 99% cyclosporine metabolites (CMs).[5] Recent studies have shown that biogradation of CsA produces a relatively small number of metabolites, some of which have been isolated from blood, bile and urine from both experimental animals and humans.[5-8] Most are lipophilic, as indicated by their occurrence in the ether phase of liquid extraction, although polar metabolites have been described. The cyclic endecapeptide structure of CsA is preserved in all identified metabolites.[3,5]

Cyclosporin A is unique in that it is not cytotoxic and is selective in its immunosuppressive effects, having particular influence on T-cell func-

tion.[9-12] Although the precise mechanism of action is controversial, it has been suggested[13,14] that the major immunosuppressive property of CsA stems from inhibitory effects on interleukin-2 (IL-2) receptor expression on activated T cells. Others[15,16] have described an inhibitory effect on DNA synthesis due to selective blockage of IL-2 production, rather than IL-2 receptor generation. The immunosuppressive effects of CsA on immune cells in vitro can be measured by the inhibition of T-lymphocyte proliferative responses induced by mitogens (e.g., concanavalin A [Con A], phytohemagglutinin [PHA]) and in a mixed lymphocyte response (MLR).

Little is known about the effects of CMs on immune responses. Maurer[3] found that CMs had low immunosuppressive effects when compared with CsA. However, Fidelus and Ferguson[17] suggested that a second immunosuppressive agent, other than parent CsA, exists in plasma. More recently Freed and colleagues[18] have reported that some purified CMs and CMs isolated from the blood of renal transplant patients have immunosuppressive properties. Because of these conflicting reports we undertook studies to identify CMs in bile, blood and urine from an orthotopic liver transplant patient, to determine their effects on Con A-induced proliferation and on a MLR and to compare their immunosuppressive activity with that of the parent compound (CsA).

Methods

Patients

Blood and urine were collected from six, normal, healthy, control patients after cholecystectomy and from a patient who underwent orthotopic liver transplantation for hepatocellular carcinoma. Bile was collected daily from the liver transplant patient and those who had undergone cholecystectomy. The former was otherwise healthy and receiving CsA intravenously (7.5 mg/kg daily) and methylprednisolone (10 to 20 mg/d) to control rejection. All samples were collected daily and stored at −70°C until assayed.

Cells

Peripheral blood mononuclear cells (PBM) were collected from the venous blood of healthy control subjects, aseptically drawn into 50 ml conical tubes containing 1.5 ml of 0.5 M citrate buffer at pH 5.0. The blood was centrifuged at 2200 *g* for 20 minutes and the plasma removed. The cells were then diluted 4:1 with RPMI 1640 medium (Flow Laboratories, Mississauga, Ont.) and centrifuged over Ficoll Hypaque gradients (1.074 g/L) at 2200 *g* for 12 minutes at 22°C, as previously described.[19] Mononuclear cells were removed at the interface (less than 1% polymorphonuclear cells), washed three times with RPMI 1640 and resuspended at a concentration of 2×10^6 PBM/ml in RPMI 1640 which had been supplemented with 10% fetal calf serum (Flow Laboratories) and 4 mM glutamine (Gibco Scientific, Burlington, Ont.).

Isolation of Cyclosporin A and Cyclosporine Metabolites

One part bile (10 ml), blood (10 ml) or urine (50 ml) was extracted with two parts diethyl ether (Fisher Scientific Co., Toronto, Ont.) three times. The ether extracts were combined and evaporated to dryness under vacuum at 45°C. The residue was reconstituted in 400 μl of the solvent system, acetonitrile:methanol:water (50:20:20) and chromatographed by high-pressure liquid chromatography (HPLC). Two methods of HPLC separation were used. In the first, a 15-cm uBondapak/C18 column and model M-45 pump (Waters Associates, Milford, Mass.) were used to separate CsA from its metabolites. Of the reconstituted residue 400 μl was subjected to chromatography on the C18 column at 50°C with a flow rate of 1.5 ml/min. Cyclosporine metabolites and CsA were collected in the first and second 10 ml respectively. The presence of metabolites and CsA was determined by radioimmunoassay[20] and the samples were dried under vacuum at 45°C. In the second method, two Beckman "ultrasphere-ocytl" 5-μm reversed phase columns (4.6 mm × 250 mm) were connected in tandem to further separate CMs. Again 400 μl of the reconstituted residue was injected and run at a flow rate of 1.0 ml/min at 70°C, and 0.5-ml fractions were collected. The presence of CMs was determined again by radioimmunoassay, and six fractions were pooled and evaporated to dryness. In the Con A proliferation assay, separate fractions were redissolved in RPMI 1640 containing 0.1% Tween 20 (Sigma Chemical Co., St. Louis, Mo.).

Concentrations of fractions containing known CMs were calculated by utilizing data on the cross-reactivity of the different metabolites in the Sandoz cyclosporine radioimmunoassay as documented in the product monograph (Table I).

Mitogenic Response to Concanavalin A

The proliferative response of PBM was assessed by culturing 4×10^5 cells with 5 μg/ml of Con A (Sigma Chemical Co.) for 72 hours in 96 well microtitre plates (Falcon 3040, Microtest II, Becton-Dickinson, Lincoln Park, NJ) at 37°C in a 5% carbon dioxide atmosphere in 200 μl of RPMI 1640 supplemented with 10% fetal calf serum and 4 mM glutamine. Cells were cultured alone or with increasing concentrations of CM or CsA. One μCi of ^{3}H-methyl thymidine (^{3}HTdR) (25 Ci/mmol) (Amersham Corp., Toronto, Ont.) was added for the final 18 hours of culture. Cells were harvested onto fibreglass filters with a minimash II cell harvester (Microbiological Associates, Bethesda, Md). The uptake of ^{3}HTdR was quantitated by placing the filters in 5 ml of scintillation fluid consisting of 10 ml of Omnifluor (New England Nuclear, Boston, Mass.) per 3.785 L toluene (Aquasol II, New England Nuclear) and by counting in a Beckman scintillation counter (Beckman Instruments Inc., Schiller Park, Ill.). The mean counts of stimulated cultures were corrected for uptake of control unstimulated cultures.

Data Analysis

Data were statistically analysed using the Student's *t*-test, and a p value of less than 0.05 was considered significant.

Results

Isolation and Fractionation of Cyclosporine Metabolites and Cyclosporin A

Cyclosporines, identified by radi-

Table I—Relationship of Cyclosporin A (CsA) and Cyclosporine Metabolites (CMs) in Radioimmunoassay (RIA)

CsA/CM	Concentrations by RIA (μg/ml)	True concentration (μg/ml)
CsA	100	910
CM1	100	1000
CM8	100	1000
CM9	100	1000
CM10	100	1000
CM17	100	670
CM18	100	710

Cross-reactivity of CMs in the RIA to parent CsA is described in the Sandimmune RIA kit (Sandoz Pharmaceuticals, Dorval, PQ).

oimmunoassay, were extracted from blood, bile and urine of the liver transplant patient and separated into total CM and CsA fractions by HPLC method 1. When the same fluids were fractionated by method 2 and analysed by radioimmunoassay, seven peaks (fractions) of cyclosporines were obtained, corresponding to the six fractions of CMs and the parent CsA (fraction 7) (Fig. 1).

Identification of CMs (7, 18 and 21) was accomplished by using internal purified CM kindly provided by G. Maurer, Sandoz, Basel, Switzerland. Metabolites 1, 8, 9, 10 were identified by HPLC/mass spectrometric analysis as previously described[21] (Table II).

Utilizing the data from Table I, true concentrations of parent CsA and those fractions containing known CMs were determined as shown in Table II. Based on these data, the concentration of total cyclosporines in the bile of the liver transplant patient was 27- and 128-fold greater than that of blood and urine respectively. Concentrations could not be established for fractions 1 and 4, which did not contain known CM.

Bile fractions 3 and 5 accounted for 80% of total cyclosporines, with CsA accounting for less than 1% of the total (Fig. 1A, Table II). Blood contained significantly ($p = 0.007$) lower concentrations of CsA and CMs, but in contrast to bile, parent CsA constituted a substantially greater proportion of the total cyclosporines (3.5%). Of the CMs in blood, 82% was localized to fractions 3 and 5, similar to that seen in bile (Fig. 1B, Table II). Small amounts of CMs and CsA were detected in urine; however, 90% of the CMs were equally distributed in fractions 2, 3 and 5, and parent CsA was 1% of the total (Fig. 1C, Table II). No cyclosporines, as measured by radioimmunoassay, were detected in bile, blood or urine extracted with diethyl ether from control subjects.

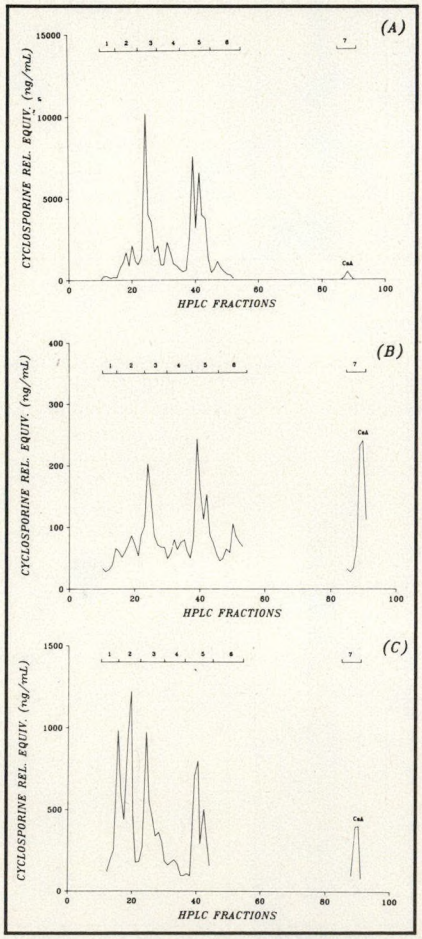

FIG. 1 — Isolation of cyclosporin A (CsA) and cyclosporine metabolites (CMs) from liver transplant patient. Cyclosporine metabolites (fractions 1 to 6) and CsA (fraction 7) were isolated from (A) 10 ml of bile, (B) 20 ml of blood and (C) 50 ml of urine and separated by high pressure liquid chromatography (HPLC) method 2. Concentrations of cyclosporines were determined by radioimmunoassay and are expressed as cyclosporine-relative equivalents (ng/ml of HPLC effluent).

Effect of Cyclosporine Metabolites and Cyclosporin A on Concanavalin A Proliferation

Marked stimulation of proliferative activity in human PBM, as reflected by ^{3}HTdR uptake, in response to Con A was noted. Maximum proliferation (115 282 ± 12 840 cpm) was seen at 5 μg/ml of Con A, as previously described.[22] Bile, whole blood and urine were assayed for their ability to inhibit the Con A proliferative response. Bile from controls significantly ($p < 0.01$) inhibited the Con A proliferative response up to a 1:32 dilution (Fig. 2A). In contrast, bile from the liver transplant patient (to a 1:1024 dilution) completely suppressed the Con A proliferative response, suggesting the presence of additional inhibitory compounds (Fig. 2A). Whole blood from normal controls inhibited Con A proliferation to a dilution of 1:64, whereas whole blood from the liver transplant patient fully suppressed Con A proliferation to a dilution of 1:1024 (Fig. 2B). In contrast, no inhibitory activity was detected in urine from either the controls or the liver transplant patient (Fig. 2C). Total CMs isolated from bile and blood exhibited dose-dependent suppression of Con A proliferation. The immunosuppressive activity of the CM fraction was similar to that of the parent CsA fraction in both fluids, indicating that a substantial portion of the immunosuppressive effect of cyclosporine was related to CMs.

The six CM fractions obtained from bile and blood by HPLC method 2 demonstrated dose-dependent inhibition of the Con A proliferative response (Figs. 3 and 4). However, different CM fractions exhibited different degrees of suppressive activity. Relative potency was expressed as the concentration required for 50% inhibition of Con A-induced proliferation (Table III). However, as fractions 1 and 4 did not contain known CMs, their concentrations could not be established accurately; thus, relative potency could not be determined. By this analysis fractions 2 (CMs 8 + 9) and 3 (CM 10) from bile and blood had similar potency to parent CsA. In contrast, peaks 5 and 6 had substantially less (5- to 20-fold) immunosuppressive activity (Table III). Fractions 1 and 4 had substantial immunosuppressive activity; however, their concentrations could not be established because their structure is unknown. Thus, relative potency could not be determined.

Discussion

The fungal metabolite cyclosporin A (CsA) is a powerful immunosuppressant and is now the major drug used to prevent rejection after organ transplantation. There is evidence that CsA is metabolized extensively

Table II—Cyclosporin A (CsA) and Cyclosporine Metabolites (CMs) in the Bile, Blood and Urine of a Liver Transplant Patient

CsA/CM	Bile, μg/L	Whole blood, μg/L*	Urine, μg/L
Total cyclosporines	237 687	887	1860
Fractions			
1 Unknown†	—	—	—
2 CMs 8, 9	33 520	86	570
3 CMs 9, 10	93 600	200	700
4 Unknown†	—	—	—
5 CMs 17, 1	97 695	528	500
6 CM 18	12 212	43	70
7 CsA	660	31	20

*For comparison the blood level for CsA by radioimmunoassay was 880 μg/L.
†As these metabolites have not been identified, concentrations could not be assigned.

by hydroxylation and N-demethylation,[3,23] and the structure of the metabolites suggests the involvement of the hepatic microsomal cytochrome P-450-dependent mono-oxygenase system.[3,5,23] The liver appears to be the major site of CsA metabolism as well as the primary excretion site by way of bile and thence fecal elimination.[8] Enterohepatic recirculation of CsA has been suggested by the appearance of two phases of CsA in radioimmunoassay pharmacokinetic profiles.[17] It has been noted that upon restoration of the integrity of the biliary system, CsA requirements are reduced.[24] This could be explained by improved intestinal absorption of CsA as well as reabsorption of CMs in bile possessing immunologic activity. Supportive of a role for CMs is a recent report[25] that bile contains primarily crossreactive metabolites with low concentrations of parent CsA.

Several CMs have been identified by chromatography. Two major oxidative metabolites, 17 and 18, have been isolated from urine, bile and blood, and both appear to express less immunosuppressive activity than CsA.[3] Lensmeyer and Fields[26] described the presence of a compound in whole blood from a renal transplant patient on CsA which cross-reacted in the Sandoz radioimmunoassay. It appeared to be localized to red blood cells, with very little detected in plasma. Fidelus and Ferguson[17] also reported the presence in the serum of renal allograft patients who were on cyclosporine of a factor that possessed potent immunosuppressive activity. Freed and col-

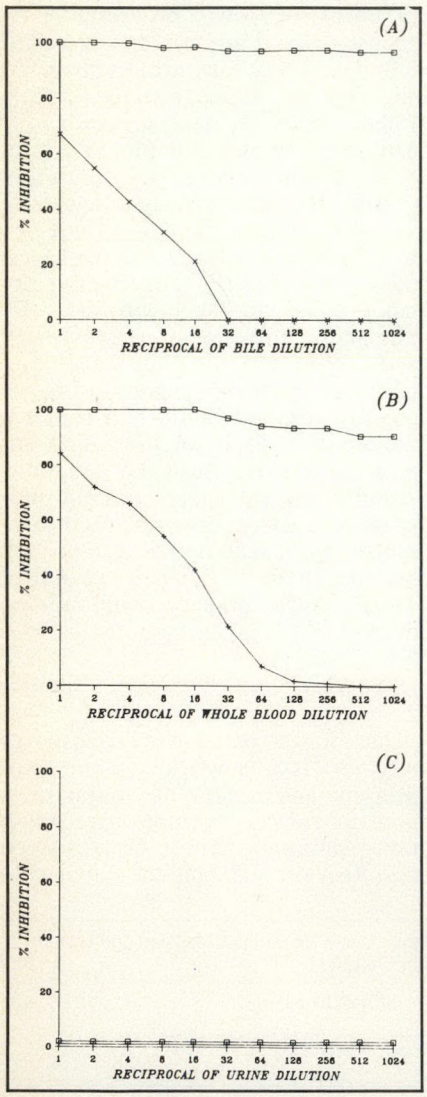

FIG. 2 — Effects of bile, whole blood and urine from normal control subject and liver transplant patient on concanavalin A (Con A)-induced proliferation of peripheral blood mononuclear cells (PBM). Dilutions of (A) bile, (B) whole blood and (C) urine from normal control (crosses) and liver transplant patient on CsA (squares) were assayed for their ability to inhibit Con A-induced proliferation of PBM.

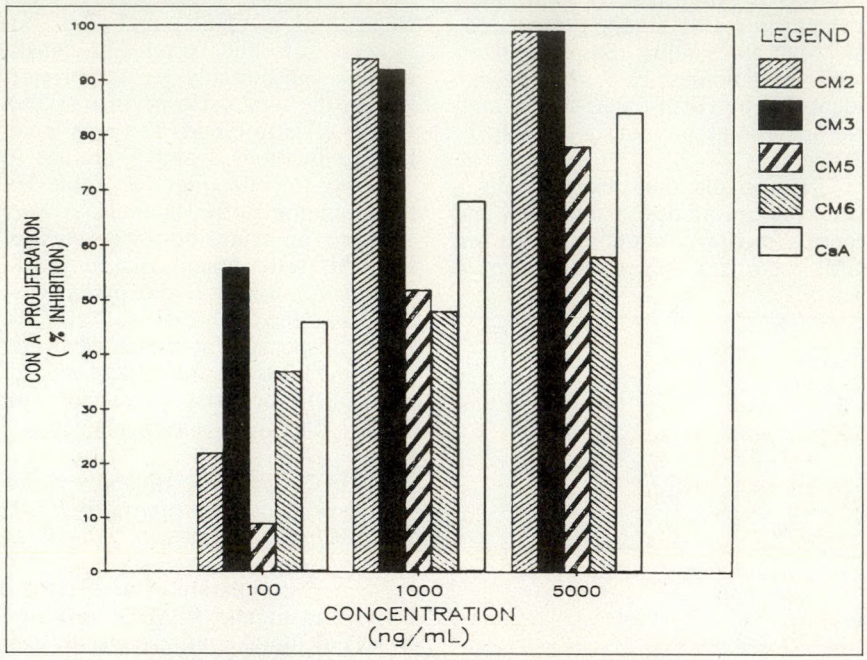

FIG. 3 — Effect of CM and CsA extracted from bile of liver transplant patient on Con A-induced proliferation. Cyclosporine metabolites (fractions 2, 3, 5 and 6) and CsA (fraction 7) isolated from bile of liver transplant patient were assayed for their ability to inhibit Con A-induced proliferation of PBM.

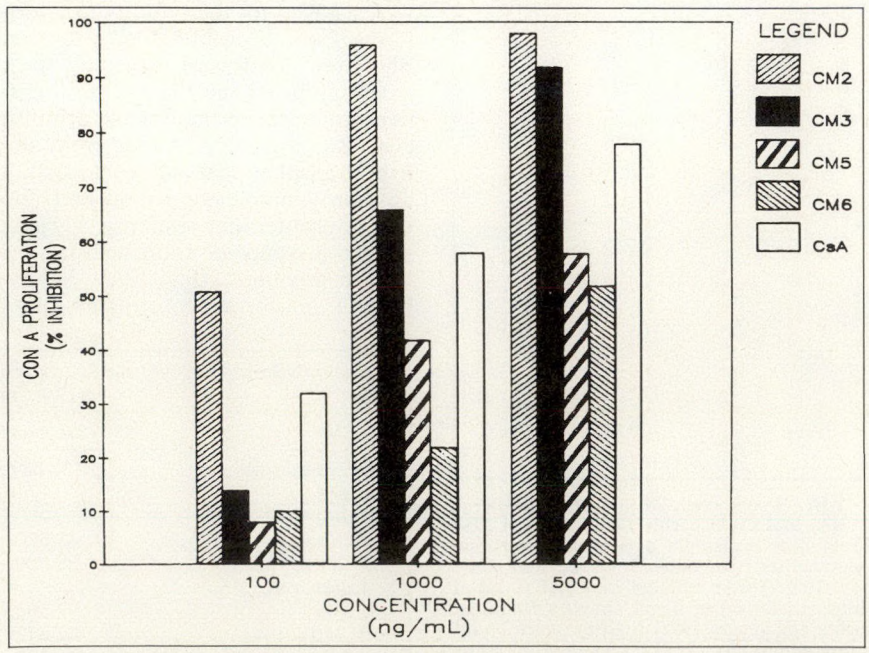

FIG. 4 — Effect of CsA and CM isolated from whole blood of liver transplant patient on Con A-induced proliferation. Cyclosporine metabolites (fractions 2, 3, 5 and 6) and CsA (fraction 7) were extracted from whole blood of liver transplant patient and assessed for their ability to inhibit Con A-induced proliferation of PBM.

leagues[18] recently reported that purified CMs 1, 17 and 21 have potent immunosuppressive activity in vitro and that CMs isolated from the blood of a renal transplant patient also exhibited significant immunosuppressive activity.

Our present studies were undertaken to document the presence by HPLC and radioimmunoassay of CMs in bile, blood and urine from a patient who had undergone orthotopic liver transplantation and to determine whether these metabolites possessed immunosuppressive activity.

Bile and whole blood from the liver transplant patient suppressed Con A-induced proliferation in dilutions at which normal bile and whole blood had no such effects, suggesting the presence of one or more inhibitory factors. Diethyl ether-soluble factors were isolated from bile, blood and urine and analysed for the presence of cyclosporines by radioimmunoassay. Although they all contained cyclosporines, immunosuppressive activity could be detected only in blood and bile with bile having significantly ($p < 0.008$) more activity. High-pressure liquid chromatography and radioimmunoassay of diethyl ether-soluble material confirmed the presence of CMs and CsA in all three body fluids, with the highest concentrations in bile as previously reported.[8,25] Significant ($p = 0.002$) immunosuppressive activity was found in both fractions of CMs and the parent CsA fraction. This suggests that, in vivo, CMs exert a marked immunosuppressive effect. Separation of the metabolites by HPLC method 2 yielded six CM fractions, two of which appeared to have immunosuppressive activity, similar to that of parent CsA. Two other fractions, 1 and 4, were also potent but cannot be assessed further until their structure is known.

Freed and colleagues[18] recently reported that CMs 1 and 17 had significant immunosuppressive activity, but that CM 8 showed little activity in both the Con A proliferation and MLR assays. As CM fraction 2 in our study showed significant immunosuppressive activity and contained CMs 8 and 9, CM 9 would also appear to inhibit both MLR and Con A proliferation.

Our radioimmunoassay method of assessing CMs does not allow for detection of those that are nonreactive in the radioimmunoassay. The presence of such metabolites will only be confirmed using tracer techniques and comparing these simultaneously to radioimmunoassasy-positive metabolites. Indeed Maurer and associates,[5] using tracer techniques, identified 17 metabolites, all of which retained their basic endecapeptide structure. This suggests that each of the six CM fractions we identified may indeed contain many more distinct metabolites. It is apparent that CMs are present in the blood of transplant patients in much greater amounts than CsA, but this has not been apparent due to differences in reactivity in the CsA radioimmunoassay.

We excluded methylprednisolone as the immunosuppressive factor in our transplant patient, both by failing to detect it in diethyl ether-extracted blood and bile, and by the fact that immunosuppression of Con A proliferation could only be detected at pharmacologic concentrations (1 μg/ml).

The observation that urinary CMs have no immunosuppressive activity, while similar fractions from bile and whole blood are strongly inhibitory, is intriguing. Although the urinary CMs are recovered from the HPLC column in the same fractions as bile and blood, they may not be identical in chemical structure. Conjugation could impair immunosuppressive activity, and although conjugated metabolites have not previously been detected,[3,4] this does not exclude their presence in this clinical setting. Finally, as previously reported,[3,8,25] only very small amounts of CMs were recovered from the urine of the transplant patient, and in order to recover the CMs, large volumes of urine (50 to 100 times the volume of bile) needed to be extracted; this may result in recovery of substances from the urine that could interfere with the immunosuppressive properties of the CMs.

Although in this study data from only one allograft recipient are presented, we have now isolated similar CM fractions from the whole blood of a renal allograft recipient that had similar immunosuppressive activity, but only when used at higher concentrations (unpublished data). The variability in immunosuppressive activity may be related to differences in CsA metabolism from patient to patient. Furthermore, we have now demonstrated that three CM fractions isolated from bile and two CM fractions isolated from blood can inhibit a mixed lymphocyte response similar to that of parent CsA, adding strength to the concept that CMs have potent immunosuppressive properties (Table IV). It is interesting that the immunosuppressive activity of some CMs differed in the two different assays; however, this has been observed for other immunosuppressive agents.

In summary, we report that bile and blood from a liver transplant patient contain CMs that have significant immunosuppressive activity, results that may help to explain why patients with similar blood levels of CsA often exhibit different degrees of immunosuppression. Furthermore, it

Table III—Relative Inhibition of Concanavalin A-Induced Proliferation by Cyclosporin A (CsA) and Cyclosporine Metabolites (CMs)

Cyclosporine fractions	Metabolite	Concentration of CMs for 50% inhibition, ng/ml	
		Bile	Blood
1	Unknown*	—	—
2	8, 9	100	250
3	10	300	100
4	Unknown*	—	—
5	17, 1	2700	1000
6	18	5000	2000
7	CsA	270	160

*These metabolites have not been identified and thus concentrations cannot be assigned.

Table IV—Relative Inhibition of a Mixed Lymphocyte Response by Cyclosporin A (CsA) and Cyclosporine Metabolites (CMs)

Cyclosporine fractions	Metabolite	Concentration of CMs for 50% inhibition, ng/ml	
		Bile	Blood
1	Unknown*	—	—
2	8, 9	90	180
3	10	75	70
4	Unknown*	—	—
5	17, 1	50	50
6	18	1000	500
7	CsA	50	30

*These metabolites have not been identified and thus concentrations cannot be assigned.

is conceivable that susceptibility to nephrotoxicity may reflect different patterns of CsA metabolism. Experiments are now under way to characterize these metabolites and determine their effects in other in-vitro and in-vivo immunologic assays. These studies should improve our understanding of the biologic behaviour of CsA.

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Prognostic Factors in Colorectal Carcinoma of Young Adults

To determine why the prognosis for colorectal cancer in young adults is poor, survival and prognostic factors in patients under 40 years of age were compared with those in patients between 40 and 50 years of age. In a 10-year period, 122 patients less than 50 years of age (88 between 40 and 50 years) presented at the Victoria General Hospital in Halifax, NS, with colorectal cancer. Their charts were retrospectively reviewed. Follow-up was obtained for all patients.

Of the 34 patients younger than 40 years, 71% (24) were men compared with 38% (33) of older patients. Symptoms, their duration and the location of primary tumours were similar in the two groups. Patients younger than 40 years presented with advanced lesions (Dukes' stages C and D) in 67% of cases compared with 52% of the older group. Mucinous tumours were twice as common in patients less than 40 years old ($p = 0.036$) and actuarial survival rates were lower at all stages for the same group.

The authors conclude that the poorer prognosis in patients less than 40 years of age is not due to late symptom reporting or delay in diagnosis, but to more aggressive disease.

Afin de déterminer pourquoi le pronostic du carcinome recto-colique chez les patients jeunes est mauvais, la survie et les facteurs pronostiques des malades de moins de 40 ans ont été comparés à ceux de patients de 40 à 50 ans. Sur une période de 10 ans, 122 patients de moins de 50 ans (dont 88 entre 40 et 50 ans) ont été reçus au Victoria General Hospital de Halifax, NE, souffrant de cancer recto-colique. Les dossiers médicaux ont été étudiés retrospectivement. Un suivi a pu être obtenu pour tous les patients.

Sur les 34 patients de moins de 40 ans, 71% (24) étaient des hommes, comparativement à 38% (33) pour les patients plus âgés. Les symptômes et leur durée, et la localisation des tumeurs primitives étaient les mêmes dans les deux groupes. Les patients âgés de moins de 40 ans présentaient des lésions avancées (stades C et D à la classification de Dukes) dans 67% des cas, comparativement à 52% pour les patients plus âgés. Les tumeurs mucineuses étaient deux fois plus fréquentes chez les patients de moins de 40 ans ($p = 0.036$) et la survie actuarielle était plus faible à tous les stades pour ce même groupe.

Les auteurs concluent que le plus sombre pronostic des patients de moins de 40 ans n'est pas dû à un retard à signaler les symptômes ou à un délai de diagnostic, mais plutôt à une maladie plus agressive.

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Colorectal carcinoma is most commonly seen in older patients, the peak incidence occurring in the seventh decade of life.[1] However, it has been reported that in 8% of cases the patient is younger than 40 years[2] and in 1% younger than 30 years.[3] There has been a long-standing impression that patients under 40 years old have a poor prognosis.[4,5] However, in recent studies identical survival rates were found for patients both under and over 40 years of age,[6-9] while others confirmed a worse prognosis for the younger group.[10-13] We undertook a retrospective study to determine if patients less than 40 years of age have a worse prognosis than those between 40 and 50 years, and also to compare the two groups in terms of symptoms and their duration, pathologic characteristics of the tumour and clinical stage.

Patients and Methods

We reviewed the charts of all patients less than 40 years of age admitted to the Victoria General Hospital in Halifax between Jan. 1, 1974 and Dec. 31, 1984 with colorectal carcinoma.

The patients were divided into two groups: group 1, 34 patients who were less than 40 years of age at the time of diagnosis and group 2, 88 patients aged 40 to 49 years. The two groups were compared with respect to diagnosis, duration of symptoms, presenting symptoms, location of the primary tumour, Dukes' stage, pathological findings and survival. The current status of all patients was noted from ongoing hospital charts or the files of the Nova Scotia Tumour Registry, or by contacting the attending physician. The date and cause of death were available for all who died. Follow-up of living patients ranged from 15 months to 135 months (mean 44 months for group 1 and 47 months for group 2). One pathologist (N.H.A.) examined the 82 original specimens available for review. The histologic grade, depth of invasion, lymph-node involvement and presence or absence of mucin were assessed for each lesion. A tumour was judged to be mucinous if it met the criteria of Symonds and Vickery.[14] The χ^2 test was used to assess apparent differences, and actuarial survival rates were calculated. A p value of less than 0.05 was considered significant.

Table I—Sex Distribution

Group	Men	Women
1	24	10
2	33	55
Totals	57	65

Table II—Presenting Symptoms and Signs*

Symptom/sign	Group 1, no. (%)	Group 2, no. (%)
Abdominal pain	8 (24)	35 (40)
Rectal bleeding	15 (44)	36 (41)
Change of bowel habit	14 (41)	34 (39)
Obstruction	5 (15)	10 (11)
Anemia	2 (6)	9 (10)
Weight loss	3 (9)	11 (13)
Mass	1 (3)	7 (8)
Miscellaneous	2 (6)	5 (6)
None	2 (6)	4 (5)

*None of the differences were significant.

Table III—Duration of Symptoms*

Duration, mo	Group 1, no. (%)†	Group 2, no. (%) ‡
< 1	10 (29)	30 (34)
1 – 3	2 (6)	15 (17)
4 – 6	11 (32)	20 (23)
7 – 12	2 (6)	12 (14)
> 12	4 (12)	4 (5)
Unknown	3 (9)	3 (3)

*No significant differences between the groups.
†2 were asymptomatic.
‡4 were asymptomatic.

Table IV—Location of Primary Tumour*

Location	Group 1, no. (%)	Group 2, no. (%)
Cecum and ascending colon	5 (15)	15 (17)
Transverse colon	1 (3)	7 (8)
Descending colon	4 (12)	9 (10)
Sigmoid	13 (38)	33 (38)
Rectum	11 (32)	29 (33)
Unknown	1 (3)	0 (0)

*No significant differences between the groups.

Table V—Dukes' Stage*

Stage	Group 1, no. (%)	Group 2, no. (%)
A – confined to bowel wall	0 (0)	3 (3)
B – penetrating serosal surface	11 (32)	39 (44)
C – positive nodes	14 (41)	29 (33)
D – distant metastases	9 (26)	17 (19)

*No significant differences between the groups.

Findings

The sex distribution of the 122 patients (Table I) was highly significant ($p = 0.002$).

Symptoms and signs of colorectal carcinoma in the two groups were similar (Table II). In both, abdominal pain, rectal bleeding and change of bowel habit were the most common complaints. Table III shows the duration of symptoms; in group 1, 74% had been symptomatic for less than 6 months compared with 78% in group 2.

There was a predominance of left-sided primary tumours (Table IV) — 82% in group 1 and 81% in group 2 were distal to the splenic flexure. One patient in group 1 had two synchronous primaries as did five patients in group 2.

The Dukes' staging was recorded at the time of diagnosis for all patients (Table V). No patients in group 1 but three in group 2 had stage A lesions.

On the other hand, more advanced disease (stages C and D) was seen in group 1 (67%) than group 2 (52%), although the difference was not significant ($p = 0.18$). Table VI shows 5-year survival rates for each Dukes' stage; again, the differences were not significant. Of 12 patients with rectal tumours in group 1, 2 survived 5 years, compared with 14 of 31 in

group 2, an insignificant difference. There was no difference in survival between the groups for patients with colonic tumours.

There was an overall similarity in the histologic grading of the tumours. Moderately differentiated lesions were present in 70% of group 1 and 82% of group 2 patients; the remainder were equally divided between poorly and well-differentiated tumours. The incidence of predisposing conditions was low — one group 1 patient with ulcerative colitis and another with polyposis coli and in group 2 two patients with polyposis coli.

With respect to actuarial survival (Fig. 1), group 1 had a lower proportion surviving at all intervals, most apparent in years 1 to 3. The number surviving at each interval was inadequate to prove statistical significance, but we can infer a poorer prognosis for younger patients from the consistently lower proportion surviving.

A review of the surgical specimens showed general agreement with the initial pathology reports. On reexamination of lymph nodes, five patients initially classified as having Dukes' B lesions were found to have Dukes' C. Classifications of lesions as mucinous or nonmucinous were not changed as a result of specimen reexamination. When the initial slides were not available, the findings on the original pathology report were used. In group 1 there were 13 mucinous and 21 nonmucinous lesions, while group 2 had 16 mucinous and 72 nonmucinous lesions ($p = 0.036$) (Table VII).

Although retrospective evaluation of their overall health is difficult, the fact that both groups of patients were composed of relatively young people (mean ages 32.3 and 46.5 years) should limit the importance of this factor. All patients who died of natural causes did so as a result of colorectal carcinoma (one committed suicide).

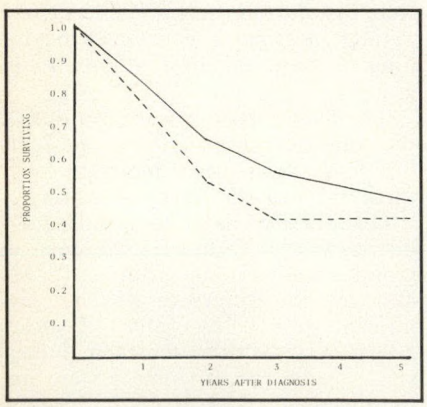

FIG. 1 — Actuarial survival. ---- = under 40 years of age (group 1), —— = 40 to 50 years of age (group 2).

Discussion

There has been a long-standing impression that young patients with colorectal carcinoma have a poorer prognosis than their older counterparts as noted by Ezzo and colleagues[13] in 1958. A study in 1974[4] found that the 5-year survival for those under age 35 was 17.5%. Sugarbaker and colleagues[5] concluded that age less than 30 years is associated with a particularly poor prognosis. A number of recent papers on the subject do not agree with this conclusion; a British study[6] found that age 40 years was not synonymous with a poor prognosis. Although they had a higher incidence of more anaplastic lesions, younger patients tolerated emergency surgery better and overall had an improved prognosis.

To limit the factor of better tolerance we reviewed two groups close to each other in age. Although the numbers are too small to show significant differences in actuarial survival, the trend to a poorer prognosis is clear.

An interesting observation is that mucin-secreting tumours were twice as prevalent in the younger group; 38% of group 1 patients had mucinous tumours, compared with 18% of group 2 ($p = 0.036$). Bedikian and colleagues[10] found an increased rate of mucin-secreting tumours in patients under 40 years of age. A study of 62 patients[11] found that colorectal carcinoma was a more virulent disease in patients under the age of 40 years, with a higher incidence of poorly differentiated lesions and mucin-secreting tumours. Adolescents with far advanced colorectal carcinoma have an extremely high percentage of mucinous lesions.[1,15]

Two Scandinavian studies that reviewed all cases of colorectal carcinoma in Denmark[8] and Sweden[9] over more than 20 years found that prognosis was not affected by age at presentation; interestingly, there was no difference in histologic type between younger and older patients. The previously cited study[6] from Britain also found no histologic difference in the tumours of both groups. It is interesting that European studies show a similar survival for younger and older patients, while American studies tend to reveal a poorer prognosis in younger patients, especially when there is an increased incidence of mucinous tumours; our results reflect the American pattern.

Fifteen percent of colorectal tumours produce large quantities of mucin and are associated with a particularly poor prognosis. The 5-year survival for such patients is 34%, compared with 53% for those with nonmucinous lesions. The poor prognosis may relate to either an increased water absorption by the mucus, encouraging malignant cell dispersal, or a mucopolysaccharide coating on the cells interfering with immunologic recognition of the malignant cells.[14]

Safford and colleagues[7] found that stage of the tumour at the time of diagnosis, rather than patient age, was the most accurate prognostic determinant. A report on United States military personnel found that patients under 30 years of age with Dukes' A or B lesions had the same prognosis as older patients, but those with stage C lesions had a much poorer outlook.[16] Patients in Hong Kong under 40 years old[17] were found to have a higher number of Dukes' C and D lesions. In

Table VI—Five-Year Survival By Dukes' Stage*

Stage	Group 1, no./total (%)	Group 2, no./total (%)
A	0 (0)	3/3 (100)
B	5/7 (71)	17/30 (57)
C	3/12 (25)	11/25 (44)
D	0/8 (0)	0/17 (0)
Overall	8/27 (30)	31/75† (41)

*Data not yet available on a large enough number to prove statistical significance.
†No. followed up for 5 years.

Table VII—Mucinous Tumours

Type of tumour	Group 1, no. (%)	Group 2, no. (%)
Mucinous*	13 (38)	16 (18)
Nonmucinous	21 (62)	72 (82)
Totals	34 (100)	88 (100)

*Difference is significant ($p = 0.036$).

our study, advanced lesions were seen more commonly in younger patients, but the difference was not significant. The histologic grade of the tumour in both age groups was similar.

The majority opinion is that the poor prognosis in younger patients is due to late reporting of symptoms and failure of physicians to investigate their complaints thoroughly.[10,15] Simstein and associates,[12] in their review of military personnel with colorectal carcinoma, found no evidence of a delay in diagnosis. Other investigators[10] have reported an average of 3 months between onset of symptoms and diagnosis. Rosato and colleagues[18] noted a greater interval between onset of symptoms and diagnosis in the young, but this did not lead to a poorer prognosis. Moreover, it has been established that there is no correlation between a delay in treatment and survival from colorectal carcinoma. Associated disorders such as ulcerative colitis, familial polyposis and familial nonpolyposis syndromes have been suggested as contributing factors in colorectal cancer, but reviews to date report a very small number of patients with these culpable conditions present simultaneously.

An interesting and unexpected finding in our study was that colorectal carcinoma in those under 40 years of age was much commoner in men. Most reports do not indicate this difference; some in fact show higher numbers of women,[20] while in others there is essentially no difference.[2,6] The one study that had a much higher number of men was that of US Army personnel.[7]

Conclusions

Patients under 40 years of age with colorectal carcinoma have a poorer prognosis than those aged 40 to 50 years, due to a tendency toward aggressive tumours that present as advanced lesions and to a larger number of mucinous tumours in these patients.

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Profound Hypothermia and Circulatory Arrest in Excision of Renal Cell Carcinoma Invading the Vena Cava

Two patients with renal cell carcinoma invading the inferior vena cava to the level of the right atrium underwent complete excision of their renal tumours. Clearance of the caval extension was accomplished using cardiopulmonary bypass, profound hypothermia and circulatory arrest. The use of these techniques visually improved the operative field without extending operating time. Profound hypothermia and circulatory arrest do not increase postoperative morbidity or mortality and offer the best opportunity for cure.

Deux patients porteurs de carcinomes des cellules rénales envahissant la veine cave inférieure au niveau de l'oreillette droite, ont subi une excision complète de la tumeur rénale. Le nettoyage de l'extension cave a été réalisé grâce à une circulation extracorporelle, une hypothermie profonde et un arrêt circulatoire. L'emploi de ces techniques a permis de dégager le champ opératoire sans prolonger la durée de l'intervention. L'hypothermie profonde et l'arrêt circulatoire n'augmentent pas la morbidité et la mortalité postopératoires et améliorent les chances d'obtenir une guérison complète.

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Renal cell carcinoma is an aggressive, locally invasive tumour that tends to invade the renal veins and subsequently the inferior vena cava.[1–5] The best opportunity for cure is offered by complete removal of the renal mass and its local extension.[3–15] It is a formidable undertaking for a surgeon

to embark on excision of a renal mass with extension into the inferior vena cava reaching to the heart. We recently experienced two such cases and found the technique of profound hypothermia and circulatory arrest to be a safe and useful adjunct, facilitating resection of the intravascular component.

Case Reports

Case 1

Routine urinalysis in a 67-year-old woman in June 1986 revealed microscopic hematuria. A subsequent intravenous pyelogram demonstrated a right renal mass and inferior vena cavography a tumour obstruction to the level of the diaphragm. Computed tomography and echocardiography confirmed the presence of a thrombus extending from the right renal vein to the right atrial–caval junction (Fig. 1). There was no evidence of metastases on physical examination, chest x-ray film or computed tomography of the chest and abdomen.

This patient gave a history of longstanding hypertension, treated with propranolol, hydrochlorthiazide and prazosin. She had undergone a hysterectomy and a cholecystectomy without complications.

The only abnormal findings on physical examination were palpable right flank fullness and a blood pressure of 205/100 mm Hg. There was no clinical evidence of caval obstruction. On admission her hemoglobin level was 9.62 mmol/L, leukocyte count 6.9 × 10^9/L, blood urea nitrogen level 5.35 mmol/L (urea) and serum creatinine value of 88.4 μmol/L (all within normal limits). An SMA-12 biochemical analysis was normal. Urinalysis showed microscopic hematuria.

Just before operation, intravenous, radial artery and pulmonary artery catheters were inserted. General endotracheal anesthesia was induced using isoflurane, fentanyl citrate and pancuronium bromide.

A small roll was placed under the right flank and the patient's skin prepared with Betadine solution. A two-team approach was used, the urology team performing a right subcostal incision and the thoracic team a median sternotomy.

The right renal artery was ligated and the renal veins were isolated. The renal mass was widely dissected, removing the kidney within Gerota's fascia and dividing the ureter well away from the mass. Regional lymph nodes and the right adrenal gland were also taken en bloc.

After renal dissection, the patient was fully heparinized and cannulated for cardiopulmonary bypass, using an aortic arch cannula, a superior vena caval cannula and a right femoral cannula. Sodium pentothal, 1.5 g intravenously, was administered over a period of 8 minutes. Cardiopulmonary bypass was begun using a membrane oxygenator and roller pump, and the patient's body temperature was lowered to 18°C as her head was packed in ice. The aorta was cross-clamped and cold blood cardioplegia was given at 20-minute intervals to protect the myocardium. When the cooling process was completed, the patient's blood was diverted into the pump oxygenator and the inferior vena cava and right atrium were opened widely.

The tumour was carefully and completely removed from within the inferior vena cava. Its entire length from the renal veins to the right atrium could easily be visualized by this approach. After excision of the caval mass, the vein was liberally irrigated with sterile water.

After cavotomy closure, cardiopulmonary bypass was reinstituted and the patient gradually rewarmed. During this period, hemostasis was assured in the bed of the excised renal tumour. Once the patient was weaned from cardiopulmonary bypass and the heparin effect reversed with protamine sulfate, the wounds were closed routinely and she was moved to the intensive care unit.

The total bypass time was 74 minutes with 40 minutes of aortic cross-clamp time. The time of circulatory arrest, however, was only 25 minutes.

The patient had no neurologic sequelae. She required eight units of packed red cells and four units of fresh frozen plasma during the postoperative period.

When she was discharged home on postoperative day 9 she had normal renal function and a hemoglobin level of 6.95 mmol/L. She was still well 22 months later.

Case 2

A 72-year-old woman was seen by her family physician for nonspecific chest and abdominal pains. There was no history of hematuria. She had lost 2.3 kg in weight over the preceding 2 months while dieting. She was taking guanethidine, ranitidine and chlorothiazide.

Abdominal ultrasonography revealed a right renal mass. Intravenous pyelography and computed tomography (Fig. 2) of the abdomen demonstrated a right renal tumour (7 cm in diameter) with extension into the right renal vein and inferior vena cava. Bone scanning and computed tomography of the chest gave normal results. Echocardiography showed the tip of a caval thrombus close to the right atrium.

Her medical history included hypertension, cholecystectomy, stroke (with recovery), myocardial infarction and arthritis of her knees. She was an obese woman with evidence of peripheral arterial disease and varicose veins. On admission she had a hemoglobin level of 7.88 mmol/L, leukocyte count of 5.4 × 10^9/L, blood urea nitrogen level 5.0 mmol/L (urea) and a serum creatinine value of 79.6 μmol/L.

She underwent resection of a right renal cell carcinoma, using the method described in Case 1, except that we found it necessary to cannulate only the right atrium for venous access.

Adherence of the tumour thrombus made it necessary to resect 8 cm of inferior vena cava, which was reconstructed using a pericardial patch.[7] The total bypass time was 68 minutes with 49 minutes of circulatory arrest.

Postoperatively, the patient had no major complications; she required 12 units of packed red cells and 2 of fresh frozen plasma and she had anorexia secondary to a prolonged ileus. She was depressed for several days, but there was no detectable neurologic deficit.

The patient was discharged home on postoperative day 12 with a hemoglobin level of 5.8 mmol/L and normal renal indices. She was placed on a 3-month course of Coumadin to prevent thrombosis of the inferior vena caval patch graft and was still well 16 months postoperatively.

Discussion

Invasion of the inferior vena cava by renal cell carcinoma is reported to occur in 4% to 10% of patients.[1-15] Tumour extension to the right atrium is less common.[4-7,9-11] Several techniques have been described for removing renal tumours that involve the renal veins and inferior vena cava,[10-14] but when the tumour thrombus extends to or above the diaphragm, the problems are much greater.[4-9,15] Intraoperative hazards include tumour embolization into the right heart or lungs, massive bleeding or incomplete clearance of the thrombus. Cardiopulmonary bypass, profound hypothermia and circulatory arrest provide a clear, dry operative

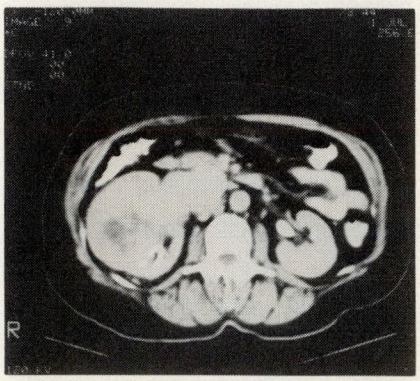

FIG. 1 — Case 1. Preoperative abdominal computed tomogram demonstrating large right renal mass extending into inferior vena cava.

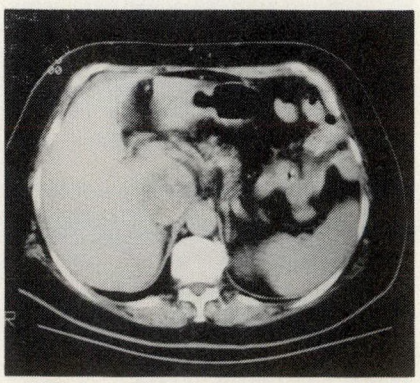

FIG. 2 — Case 2. Preoperative abdominal computed tomogram showing tumour thrombus within enlarged inferior vena cava.

field with excellent visualization of the entire suprarenal inferior vena cava, maximizing the opportunity for complete tumour resection.[6]

One potential hazard associated with this technique is the effect of cardiopulmonary bypass and profound hypothermia on hemostasis.[16] With the aid of packed red cells and specific clotting factors, we have not found bleeding to be a problem using this method. It is also possible that the routine postoperative use of desmopressin could further reduce perioperative blood loss.[17] There is concern that circulatory arrest may cause a serious neurologic deficit. The "safe" time limit for circulatory arrest is controversial,[18,19] but it would seem that the time should be kept under 40 minutes whenever possible. Whether certain anesthetic and pharmacologic maneuvers can be employed to protect the brain during circulatory arrest is unclear at present. As Hickey and Anderson[20] have noted, "the incidence of significant neurologic sequelae using modern techniques is difficult to distinguish from the incidence of cardiopulmonary bypass-related neurologic complications".

The use of pentothal, 15 to 30 mg/kg, with profound hypothermia has been shown to produce an isoelectric electroencephalogram, thereby decreasing cerebral oxygen consumption to 50% of that at normothermia.[21,22] To optimize cerebral protection, both patients received 20 mg/kg of pentothal 10 minutes before circulatory arrest. Potential side effects from the pentothal, such as prolonged sedation and myocardial depression, were not evident. Both patients remained hemodynamically stable during the rapid pentothal administration; neither required vasopressors at the end of cardiopulmonary bypass and both were extubated the morning after surgery.

Renal cell carcinoma is an aggressive lesion in which surgical extirpation remains the only treatment.[1-6] Poor prognostic features of this disease include invasion of the perinephric fat, lymph-node involvement and histologic evidence of spindle-cell formation.[23,24] Until recently, it was believed that inferior vena caval involvement conferred a poor prognosis, a view strengthened by the staging system of Robson and associates,[25] which defines renal vein and inferior vena caval involvement as a stage III lesion. Other studies have indicated that caval involvement may not be as serious as lymph-node invasion, and that survival of a patient with caval involvement alone may approximate that of a patient with a stage I lesion.[23,24]

These data reflect the aggressive nature of this disease, yet a carefully planned, well-executed operation offers the best opportunity for cure or palliation. We believe that the addition of cardiopulmonary bypass, profound hypothermia and circulatory arrest significantly increases the ease of the operative procedure with acceptable morbidity.

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Symposium on Mesenteric Ischemia

W.G. JAMIESON, MD, FRCS, FRCSC, FACS

1. Acute Intestinal Ischemia

Massive acute intestinal ischemia, an intra-abdominal catastrophe, is associated with a high death rate. Only with early diagnosis and prompt aggressive management can this rate be reduced.

The key to diagnosis is suspicion followed by intelligent interpretation of physical findings, awareness of the importance of elevated leukocyte count and inorganic phosphate levels and of acidosis, and more liberal use of superior mesenteric angiography in cases of possible intestinal ischemia. A "golden period" exists in which the bowel may be revascularized without tissue loss, so the aim should be to make the diagnosis more often during this period and to restore intestinal blood flow promptly.

L'ischémie massive intestinale aiguë, véritable catastrophe intra-abdominale, est reliée à une mortalité élevée. Seuls un diagnostic précoce et une intervention agressive rapide permettent de réduire ce taux.

La clef du diagnostic tient dans sa présomption, puis dans l'interprétation intelligente de l'examen physique, dans la reconnaissance de l'importance d'un compte leucocytaire élevé, des taux de phosphate inorganique et d'une acidose, et dans une utilisation plus répandue de l'angiographie mésentérique supérieure dans tous les cas d'ischémie intestinale possible. Il existe un "intervalle privilégié" au cours duquel l'intestin peut être revascularisé sans qu'il y ait de perte tissulaire. On doit donc tendre à faire le diagnostic durant cette période et à rétablir la circulation sanguine intestinale promptement.

Acute mesenteric ischemia has been the *bête noire* of acute abdominal conditions. The impending intraperitoneal catastrophe is out of keeping with the patient's often vague complaints, the paucity of physical findings and the lack of diagnostic help from routine laboratory investigations and plain abdominal x-ray films.

The subject I shall discuss is *massive* acute intestinal ischemia; I shall not consider small areas of necrosis, ischemic colitis, necrotizing enterocolitis of children, celiac or inferior mesenteric artery problems.

Etiology

There are three possible causes of acute mesenteric ischemia: embolism, thrombosis and nonocclusive mesenteric insufficiency.

An embolus to the superior mesenteric artery accounts for 25% to 30% of cases of acute intestinal ischemia.[1] Most (90% to 95%) emboli arise from the heart, usually because of atrial fibrillation, but also from mural thrombus in the left ventricle. Other sources of emboli may be atherosclerotic plaques and vegetation or thrombi on valves. The embolus lodges in the superior mesenteric artery a few centimetres from its origin and usually spares the middle colic artery and proximal jejunal branches, giving a classic distribution of ischemia at the time of laparotomy.

Thrombosis of the superior mesenteric artery, usually associated with aortic atherosclerosis, occurs at the origin of the vessel and involves all branches of the superior mesenteric artery, including the middle colic and early jejunal branches. The gut becomes ischemic from the duodenum to the middle of the transverse colon.

Nonocclusive mesenteric insufficiency is the term used for cases with no mechanical blockage of the superior mesenteric artery. In the majority of such patients a major contributing factor, such as cardiac failure or arrhythmia, digitalis abuse, hemoconcentration following diuretic therapy and other systemic debilitating diseases, leads to a reduction in cardiac output and subsequently in mesenteric flow. The true frequency of this problem remains unknown because the underlying cause is often corrected with return of blood flow and function of the gut.

Diagnosis

The key to early diagnosis is suspicion, especially during the first few hours when the findings are only vague abdominal pain with diffuse tenderness, anorexia and abdominal fullness.

The classic picture of obvious cardiac disease, sudden severe abdominal pain and spontaneous defecation is usually not present. I believe the onset often is insidious and early diagnosis is most difficult.

Help may be obtained from a triad of laboratory observations.

- The leukocyte count is usually grossly elevated.[2]
- Metabolic acidosis is usually present; our group likes to call this "inappropriate acidosis" as the pa-

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tient has no other obvious cause of the acid-base upset and early on is not as ill as the acidosis would indicate.[3]

- We have shown that the level of serum inorganic phosphate is substantially elevated in peripheral blood, at a time when prompt restoration of mesenteric blood flow is gut-sparing. In 20 of our cases the finding of an elevated serum phosphate level has been an accurate reflection of gut ischemia.[4-6]

I recommend that if there is *any* chance of intestinal ischemia, the serum phosphate level, leukocyte count and pH should be measured. If these are abnormal, the patient should quickly undergo superior mesenteric artery angiography and appropriate action should be taken.

With nonocclusive mesenteric insufficiency suspicion again is the key. A patient with a deteriorating cardiac problem and vague abdominal complaints whose abdomen feels "doughy" should undergo the same laboratory investigations followed by angiography. If the superior mesenteric artery spasm is not treated, the cardiac problem is magnified and often irreversible.

Treatment

Superior Mesenteric Artery Embolus

Embolectomy and resection of the necrotic bowel should be performed promptly. Attention to the source of the embolus and elimination of the cause is mandatory. Metabolic acidosis, if present, should be corrected. As soon as the diagnosis is made, heparin should be given systemically to help prevent a second embolus from dislodging and to stop propagation of the clot within the superior mesenteric artery.

Some[7] believe that the angiographic catheter should be left in the superior mesenteric artery and used to infuse papaverine (60 mg/h) because spasm is associated with the embolus and its extraction.

The superior mesenteric artery is found at the base of the mesentery as it courses over the third part of the duodenum. The embolus is removed using a small Fogarty catheter, the artery is irrigated distally with heparinized saline and the arteriotomy is closed. Obviously necrotic bowel should be resected and the viability of the remaining bowel examined. Doppler probes are available[8] and fluorescein dye tests have been helpful.[8] We use observation and Doppler examination.

Areas of bowel that are of questionable viability should be examined at a "second look" operation 24 hours after the first.[9] There are no tests to determine small areas of necrotic bowel and too much is at stake to adopt a "wait and see" attitude.

Superior Mesenteric Artery Thrombosis

Ischemic bowel extending from proximal jejunum to the splenic flexure is diagnostic of superior mesenteric artery thrombosis.

The same urgency is required for this condition as for embolism — that is, prompt surgery; I have had no experience with fibrinolytic agents.

After the artery has been isolated, it is opened at a soft spot. Removal of the thrombus with a Fogarty catheter may be attempted, but often it is to no avail. I believe that a simple bypass (aorta–superior mesenteric artery or iliac artery–superior mesenteric artery) using vein or synthetic material is the operation of choice. Aortic superior mesenteric endarterectomy, distal superior mesenteric artery–iliac artery anastomosis and axial aorta–superior mesenteric artery grafting have all been done with good results. As with the superior mesenteric artery embolus, the bowel is observed, resected if necessary and a second look laparotomy done, if indicated.

Nonocclusive Mesenteric Ischemia

Pharmacologic treatment is the mainstay of management in these patients. The angiographic catheter is left in the origin of the superior mesenteric artery and papaverine (60 mg/h) is infused for 24 hours. Repeat angiography is done and if the splanchnic circulation is normal, the catheter is removed.

If there is residual spasm, vasodilator therapy is continued for an additional 24 hours. During this 24- to 48-hour period, aggressive cardiac resuscitation is carried out.[10]

Comment

Early diagnosis is mandatory for successful management of mesenteric ischemia.

A number of points should be emphasized.

- The condition, if treated early, will give excellent results with no loss of bowel.
- Visible peritonitis with mesenteric ischemia usually indicates necrotic bowel.
- The leukocyte count is usually elevated.
- An elevated serum inorganic phosphate level in peripheral blood may be an early key to diagnosis in the patient with minimal abdominal findings.
- Superior mesenteric angiography should be used liberally if there is any possibility of acute intestinal ischemia.

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continued on page 201

C.R. LYE, MD, FRCSC

2. Chronic Mesenteric Ischemia

Although chronic mesenteric ischemia is an infrequent, even rare, condition and a busy vascular surgeon may encounter only one such patient in a year, the associated morbidity and mortality are high, especially if the condition is not recognized. General and vascular surgeons must bear in mind the triad of postprandial pain, weight loss and diarrhea. Patients with mesenteric ischemia are at high risk and generally have diffuse peripheral vascular disease. Although surgery is hazardous, successful repair can result in long-term survival without morbidity. The author favours antegrade supraceliac bypass grafting over infrarenal grafting which is technically more difficult.

L'ischémie mésentérique chronique est peu fréquente, voire rare. Un chirurgien vasculaire occupé peut n'en recontrer qu'un seul cas annuellement. Néanmoins, la morbidité et la mortalité qui y sont rattachées sont élevées, surtout quand l'affection n'est pas rapidement reconnue. Les chirurgiens vasculaires et généraux doivent garder à l'esprit la triade: douleur post-prandiale, perte de poids et diarrhée. Les patients qui souffrent d'ischémie mésentérique sont des sujets à risque et ils ont généralement une vasculopathie périphérique disséminée. Même si la chirurgie est risquée, une réparation réussie peut résulter en une survie prolongée, exempte de morbidité. L'auteur préfère un pontage supra-coeliaque antérograde à une dérivation sous-rénale, laquelle est techniquement plus difficile à réaliser.

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Reprint requests to: Dr. C.R. Lye, Associate Professor, Department of Surgery, Health Sciences Centre, 700 William Ave., Winnipeg, Man. R3E 0Z3

Chronic mesenteric ischemia is uncommon, but the associated morbidity and mortality are high. It is a manifestation of atherosclerotic occlusive disease, usually involving a combination of two or three of the following: the celiac axis and superior and inferior mesenteric arteries. Rarely, fibromuscular disease in the young or Buerger's disease in the adult may be causative, and very occasionally patients will have symptoms with single-artery involvement (usually the superior mesenteric artery). Interestingly, women are affected more frequently than men. The atherosclerotic lesion usually involves the proximal centimetre of the vessel and may be considered an extension of adjacent aortic atheroma. Although atherosclerotic involvement of the aortic orifices of the visceral vessels is common, the functional effects of single- and even double-vessel lesions are limited, due to the excellent potential collateral pathways that exist between the celiac axis and the superior mesenteric artery (pancreatoduodenal arteries), and the superior mesenteric and inferior mesenteric arteries (the arc of Riolan and marginal artery of Drummond). Usually all three vessels are involved in the symptomatic patient. The ensuing ischemia results in postprandial pain and often malabsorption, both of which may lead to weight loss. Malabsorption may lead to diarrhea which is often fatty. The end result, as noted by Dunphy,[1] is often gut infarction and death.

Clinical Presentation and Diagnosis

Pain is virtually universal in patients with chronic mesenteric ischemia. It usually develops 10 to 30 minutes after eating. It may be steady or colicky, is usually periumbilical and often varies in duration with the type and amount of food ingested. The patient learns to avoid large meals and may experience sitophobia, resulting in weight loss which may be massive and mimic carcinomatosis. In extreme cases, abdominal pain may be virtually continuous, analogous to rest pain in the extremity, and the clinical picture can merge into one of acute mesenteric ischemia. Although diarrhea is the classic form of bowel disturbance, it occurs in only 50% of patients. Constipation may also occur.

Physical findings are few. Weight loss is usually marked. Generalized atherosclerotic occlusive disease is frequent and an epigastric bruit is usually present.

The correct diagnosis is generally not made until the patient has had symptoms for many months. General abdominal x-ray films are of little value. Assessment of gut function with xylose uptake and fecal fat measurements is useful if the findings are positive, but they are frequently normal. Diagnosis depends on the clinical picture and awareness and is confirmed by angiography. Although frontal aortography usually demonstrates collateral channels, lateral views are essential to delineate the proximal celiac and superior mesenteric lesions.

Treatment

Treatment is by surgical reconstruction. Although we have had short-term success in one instance of balloon angioplasty of the superior mesenteric artery, there is no reason to expect that the outcome of angioplasty of stenoses at the origins of the visceral vessels will differ from the rather dismal results seen in similar lesions of the renal arteries.

Reconstructive techniques have been many and varied. Local short endarterectomy and patching through an anterior transabdominal approach can be applied to any of the visceral vessels and has stood the test of time.

Thromboendarterectomy of the superior mesenteric artery can be accomplished either above, through the gastrohepatic ligament, or below, through the ligament of Treitz. The retroperitoneal "trap door" approach recommended by Stoney and associates[2] affords an excellent repair, which can include the renal arteries when necessary, but demands a high level of technical expertise and familiarity with the anatomy involved. It is not for the occasional operator.

Because of its relative simplicity, the bypass graft remains the choice of most surgeons. Here the major choice lies between an infrarenal or supraceliac location for the origin of the graft. In our experience, and that of others,[3] the long retrograde infrarenal graft taken through the mesentery to the middle of the superior mesenteric artery, whether vein or prosthesis, is difficult to position and is susceptible to both early and late occlusion, often with disastrous results. A short retrograde infrarenal graft to the proximal superior mesenteric artery, where possible, is more durable. This may be technically more difficult, particularly in the patient who has previously undergone aortic surgery. Our procedure of choice is the antegrade supraceliac graft that can be brought down either in front or behind the pancreas to the middle of the superior mesenteric artery. In the very thin patient with a mobile pancreas it is possible to retract the pancreas inferiorly and accomplish the entire repair through the divided gastrohepatic ligament. This is a durable procedure,

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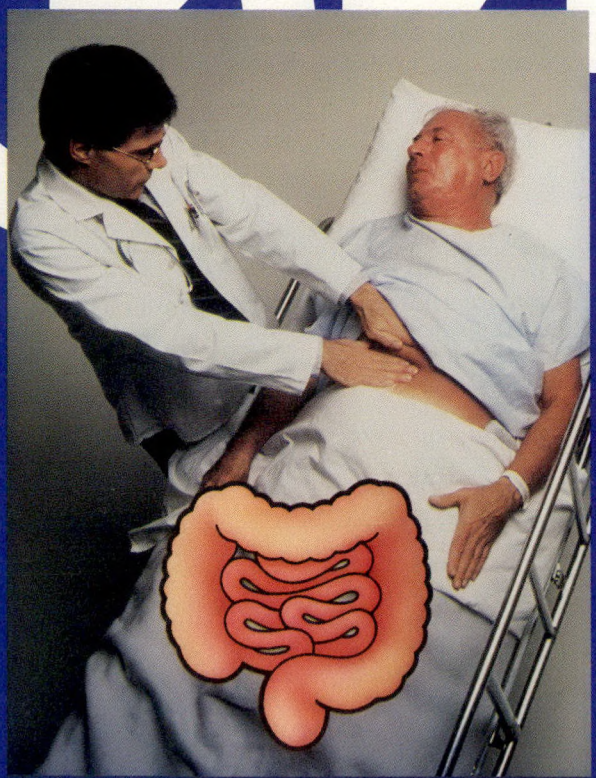

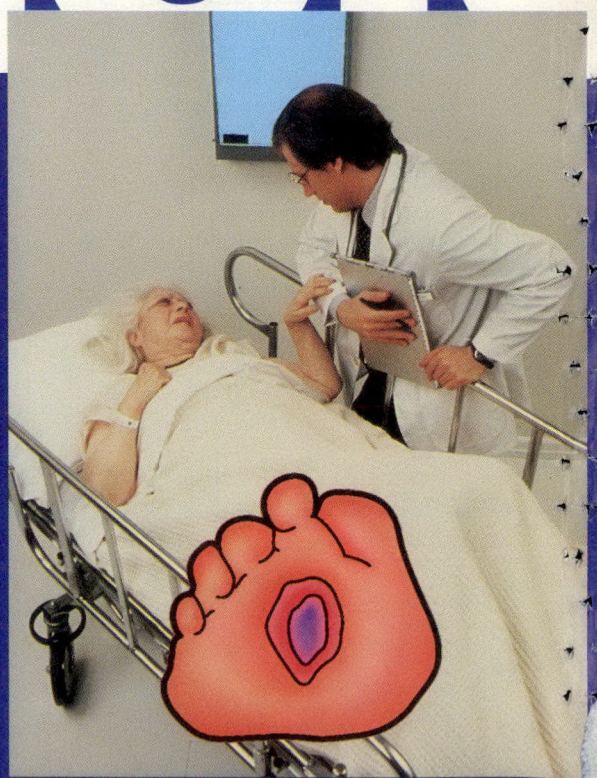

probably because of the axial orientation of the graft. If the celiac axis is involved as well as the superior mesenteric artery, the proximal anastomosis may be placed across the celiac axis as a patch angioplasty. This technique is equally applicable to the previously reconstructed aorta, and the aorta at the supraceliac level is usually free of atheroma. If a supraceliac graft is to be combined with infrarenal aortic surgery, the visceral repair should be done as the initial step.

Symptoms of mesenteric ischemia may be difficult to identify in the abdomen postoperatively, and for this reason angiography is mandatory if there is any concern in the first few days after surgical repair. In any event, angiographic assessment of the visceral vessels should be obtained before the patient is discharged from hospital.

Successful reconstruction is associated with alleviation of symptoms and the patient's return to his usual weight. As with other reconstructions, late occlusion can occur, and later abdominal symptoms should be aggressively investigated to forestall potential gut infarction.

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PETER D. FRY, MD, FRCSC, FRCS(I)

3. Colonic Ischemia After Aortic Reconstruction

Colonic ischemia after aortic reconstruction is rare, but when it occurs in its worst form it carries a 50% death rate. The etiology and pathogenesis of this condition demonstrate that in many instances it may be prevented. Early recognition, particularly of the transmural ischemic injury, is essential.

Numerous techniques used during surgery for assessing the adequacy of colonic perfusion have been evaluated and found to be cumbersome and inaccurate in terms of predicting colonic ischemia. Recent experience with the use of the pulse oximeter appears promising in identifying patients with inadequate colonic perfusion who may then be candidates for reimplantation of the inferior mesenteric artery.

L'ischémie colique consécutive à une reconstruction de l'aorte est rare. Toutefois, lorsqu'elle survient, elle entraîne, dans sa forme la plus grave, une mortalité de 50%. L'étiologie et la pathogénèse de cette affection démontrent que dans plusieurs cas elle pourrait être prévenue. Son identification précoce est essentielle, particulièrement lorsqu'on est en présence d'une lésion ischémique transmurale.

On a évalué plusieurs techniques utilisées en salle d'opération pour établir la capacité de perfusion colique. Ces techniques sont souvent lourdes et elles manquent de précision pour prédire l'ischémie colique. L'utilisation récente de l'oxymètre à impulsion paraît prometteuse pour identifier les patients souffrant d'une perfusion colique insatisfaisante qui pourraient être candidats à une réimplantation de l'artère mésentérique inférieure.

Colonic ischemia after aortic procedures is mainly iatrogenic. In its worst form, ischemic colitis complicating aortic surgery carries a 50% mortality. It is apparent, however, that vascular surgeons now have the techniques to recognize the potential for this condition and to avoid it completely.

Historical Perspective

Only 2 years after Dubost and colleagues[1] resected the first aortic aneurysm in 1952, Moore[2] reported the first case of ischemic colitis after aortic reconstruction. Since then, numerous case reports and series have been published.[3-6]

These series provide evidence of marked differences in the incidence of this condition.[3-6] In retrospective studies, an occurrence rate of 2% has been found, usually associated with an unfavourable outcome; in prospective series, the frequency was from 7% to 35% mainly because of better diagnosis through colonoscopy in the postoperative period. In 75% of cases the condition is associated with ligation of the inferior mesenteric artery during aneurysm resection; the other 25% occur during aortoiliac reconstruction for claudication.

A 12% incidence of ischemic colitis is associated with ruptured abdominal aortic aneurysm in retrospective studies. However, routine postoperative colonoscopy will reveal demonstrable mucosal changes in 60%. The death rate for elective aortic procedures has declined to approximately 2% and a similar incidence of clinically overt ischemic colitis would not be considered high. However, for the number of aortic procedures that are done in Canada, for example, 2% represents a sizable number of patients and 50% of them will die of complications associated with ischemic colitis.

Johnstone and Scobie,[7] reporting on the Canadian Society for Vascular Surgery Multicentre Study of Aneurysmectomy, demonstrated one of the lowest rates of this complication ever recorded — 0.6% in 666 patients — but the series excluded patients with ruptured aneurysms. In this series the inferior mesenteric artery was reimplanted in 4.8% of patients and carried a greatly increased incidence of hemorrhage postoperatively. Twelve percent of patients had complete exclusion of the hypogastric vessels, and in this group the frequency of both diarrhea alone and ischemic colitis was markedly increased.

In the four patients who had ischemic colitis, wound infection, paralytic ileus and renal dysfunction were also common, as might be expected. Two died, giving a death rate that was consistent with those of other published series.

Etiology

Although most documented cases of ischemic colitis are associated with ligation of the inferior mesenteric artery during the aortic procedure, associated factors contribute significantly.[3-6] Arrthymias affecting cardiac output, aortic clamp time, colonic distension, hypogastric exclusion, hypovolemia and retractor injuries have all been cited as contributing causes.[3,4]

As well, operative measures will prevent complications. Improper ligation of the inferior mesenteric artery distal to its first bifurcation could be prevented by transfixion within the sac of the aneurysm. Limiting manipulation of the aneurysm may prevent trash colon and trash foot. Also, if it is considered necessary to evacuate the retroperitoneal hematoma from the mesentery, it should be done from the lateral aspect rather than through the sigmoid mesentery. Hypogastric flow should be preserved whenever possible and this is feasible in 90% of cases.

To avoid unnecessary reconstruction of the inferior mesenteric artery, particularly when the hypogastric ves-

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sels are not going to be reperfused, measurement of colonic perfusion by one of several techniques should be considered.

Anatomical Considerations

If the principal cause of ischemic colitis is ligation of the inferior mesenteric artery and the problem is failure to recognize this dominant vessel, the solution must lie in attempting to predict the patient who requires reconstruction of the hemodynamically important inferior mesenteric artery at the time the initial aortic procedure is performed.

Collateralization between the superior mesenteric artery, its midcolic branch and the hypogastric arteries through the middle and inferior rectal arteries and the superior rectal branch of the inferior mesenteric artery is well known. The origin of the inferior mesenteric artery and its first branch, 3 to 4 cm from the aorta, can vary, and the presence of a particularly large abdominal aortic aneurysm can shorten this distance considerably. Ligation in this event can readily include the superior rectal branch or the ascending branch of the inferior mesenteric artery which together form part of a meandering mesenteric vessel. Many pseudonyms have been attached to this vessel, perhaps explaining the confusion related to the true functional anatomy of the region.

Potentially present in 60% of the general population, the meandering mesenteric vessel is identified in 30% of angiograms performed for occlusion or aneurysmal disease and is a cardinal sign, the implications of which the surgeon must not overlook.

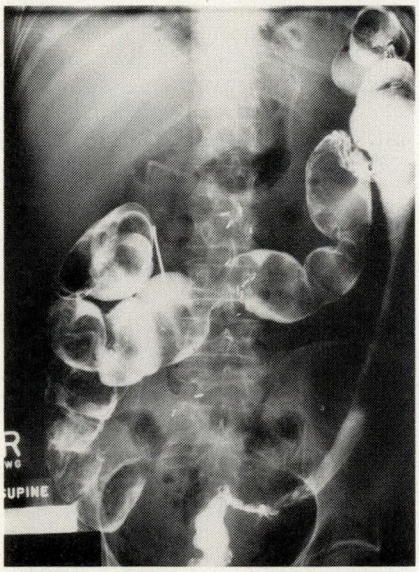

FIG. 1 — Barium enema demonstrating stricture resulting from type B ischemic insult.

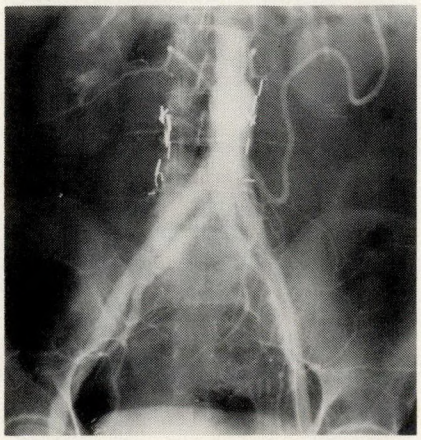

FIG. 2 — Aortogram demonstrating meandering mesenteric vessel after aortic reconstruction.

Classification

Experience has taught us to differentiate three clinicopathological types of ischemic insult, each characterized by different prognostic features.

Type A is associated with a contained, generally mild, mucosal injury from which the patient should recover normally. This is the most common type and the one most likely to be seen during colonoscopy done after aortic reconstruction.

Type B (Fig. 1) indicates an ischemic insult to mucosa and underlying muscularis; the latter lesion may produce long-term problems with insidious diarrhea and possibly stricture formation.

Type C represents the transmural ischemic injury, usually producing fairly obvious signs within a short time. Clinical signs, however, may be masked in the early postoperative period, delaying the diagnosis and resulting in increased mortality. Overt sepsis, gangrene of the colon and perforation are anticipated sequelae.

Clinical Recognition

Acute clinical awareness of ischemic colitis contributes to an early diagnosis, but with a frequency of only 2% this is not always easy to achieve, many cases not being detected as soon as they could be.

Early after aortic surgery, patients may exhibit pain, guarding, febrile episodes, oliguria and leukocytosis, features that are also typical of ischemic colitis.

Although bloody diarrhea is recognized as pathognomonic of this condition, it may not become evident for several days after the initiating insult. The decision to intervene surgically is never easy. Intervention too early may result in an unnecessary laparotomy at best or an unnecessary colonic resection with all its attendant risks at worst.

Intervention too late in a patient with a type C lesion is associated with a 90% mortality. One can argue strongly in favour of routine colonoscopy in the postoperative period. Even performed at the bedside, it has been shown to be sensitive in identifying early mucosal changes. The diagnosis can be ruled out in a sick patient if colonoscopy performed to the level of the descending colon demonstrates a normal appearance.

Barium enemas in the presence of ischemic colitis are fraught with the danger of perforation and subsequent peritonitis and are to be condemned.

Prevention

The key to prevention lies in recognizing the basic vascular abnormality. This can be achieved by identifying preoperatively patients most at risk for ischemic colitis and confirming during surgery any altered blood flow to the colon.

Angiography

It is important that vascular radiologists place their catheters high enough in the aorta to demonstrate patency of the superior mesenteric artery. If this vessel is not demonstrated angiographically,[5] one cannot be certain about its complicity in the blood supply of the colon.

If a meandering mesenteric vessel is demonstrated (Fig. 2), it may indicate obstruction of either the celiac or superior mesenteric artery. If, however, it appears on the superior mesenteric artery injection, the risk of producing ischemic colitis by ligating the origin of the inferior mesenteric artery is minimal, unless ligation occurs too far distally, which might happen in association with a particularly large aneurysm. Although angiography is standard for assessing aortoiliac disease, it is not for aneurysmal disease. In fact, we may be moving away from not only standard angiography but also intravenous and intra-arterial digital subtraction angiography. In our efforts to reduce risk factors we have become more selective in our use of contrast studies,[5] using them only when we are concerned about aneurysmal involvement of the renal arteries, associated renovascular hypertension and claudication. However, this may prevent us from obtaining important information about visceral blood flow.

When digital subtraction angiography is used, it will seldom provide adequate information regarding flow in the mesenteric arteries.

The accepted standard in many centres is now computed tomography, but magnetic resonance imaging is starting to play a similar role. Although either approach adds to the surgeon's knowledge of specific anatomy pertinent to the aneurysm, both fail to provide information about visceral flow. Duplex scanning of the superior mesenteric artery in conjunction with computed tomography or magnetic resonance imaging may correct this shortfall.

Assessing Perfusion of the Colon

It seems clear that prevention lies in recognizing the potential for ischemic colitis in the individual patient and that the ability to predict clinically the adequacy of colonic perfusion is unreliable. Current techniques for assessing perfusion in the operating room tend to be time-consuming, cumbersome, subject to equipment and human error and, thus, unreliable.

Isotope scanning,[8] although reliable, is cumbersome in the operating room. It could be more informative in the recovery period in questionable cases. Surface temperature determinations and dye injection are generally considered unreliable. Measurements of stump pressure and the inferior mesenteric artery systolic ratio have been found helpful[5,9] and are good predictors of adequate colonic perfusion when the stump pressure exceeds 40 mm Hg or when the ratio exceeds 0.4:1.

These measurements can be difficult to obtain, however, particularly in aneurysmal disease where the inferior mesenteric artery at its origin is occluded in 45% of cases.

Mucosal pH measurement with intraluminal balloon catheters in the colon, as described by Fiddian-Green and associates,[10] is a sensitive and reliable means of assessing and preventing ischemic colitis. However, it is also cumbersome and is unlikely to be available outside tertiary or quaternary care hospitals.

Thus, we need instrumentation that is sensitive, reliable, inexpensive, not time-consuming and readily available in regional hospitals where aneurysm surgery is usually carried out.

The pulse oximeter is standard equipment for the anesthetist in any hospital likely to undertake aortic surgery. It accurately measures pulsatility and oxygen saturation and, although normally attached to an appendage such as finger or nose, it readily adapts to the surface of the colon or small bowel.

Once the pulse oximeter is calibrated by the anesthetist at the start of surgery, movement of it between the finger and colonic surface back to the digit will not change its accuracy. Under normal circumstances of adequate perfusion, the recordings made by the anesthetist should mimic those obtained from the colon or small bowel. The oximeter probe is placed in a sterile sleeve and is passed into the operative field to be attached to the segment of bowel in question. Arterial pulsatility and transcolonic oxygen saturation can be measured before and after aortic reconstruction or during temporary clamping of the inferior mesenteric artery or iliac vessels.

Ouriel and colleagues[11] described their findings using this technique in 30 consecutive patients who underwent aortic reconstruction. In two patients who demonstrated loss of pulsatility with unmeasurable transcolonic oxygen saturation but without signs at surgery of impaired perfusion in the colon, classic evidence of mucosal ischemic changes was seen on colonoscopy and clinical signs of mild colitis were noted in the postoperative period. This test, although carried out in a small group of patients, appeared to be accurate in predicting viability of the colon and the need for revascularization of the patent inferior mesenteric artery.

Protocol for Identifying the Potentially Ischemic Colon

If one could reliably identify the subset of patients who, depending on inferior mesenteric artery blood flow, are clearly at particularly high risk for ischemic colitis, selective inferior mesenteric artery revascularization could be performed and adequate colonic perfusion restored in this group of patients.

The following protocol is suggested.

- Preoperative ultrasonography, which generally has routinely been done, should be followed by computed tomography or magnetic resonance imaging in the case of an aortic aneurysm, with angiography being added in selected cases. Angiography clearly is obtained in all cases of aortoiliac disease but must in addition show details of the superior mesenteric artery.
- Patients with aneurysms who do not undergo angiography should have duplex scanning of the origin of the superior mesenteric artery.

At the time of aortic reconstruction when the possibility of colonic ischemia is present, several options are available but are not necessarily equally desirable.

- First, one may proceed with reimplantation of the inferior mesenteric artery. This increases the operating time and adds the risk of anastomotic complications. It is an approach that I do not believe is justified as a routine add-on procedure. My belief has been confirmed by the Canadian Aneurysm Study.[12]
- Second, one may ignore the possibility of colonic ischemia and proceed with aortic reconstruction. If the colon is not going to be assessed and monitored during surgery, colonoscopy should be carried out routinely in the postoperative period.
- Third, my own preference is to either measure inferior mesenteric stump pressure or use the pulse oximeter to assess perfusion. If colonic perfusion is adequate, the primary aortic procedure may be performed. If the hypoperfusion of the colon is confirmed, the inferior mesenteric artery should be reconstructed using one of several well-established methods.[4,6,9]

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Methyldopa Hypersensitivity Can Mimic Acute Toxic Enterocolitis

The most widely known hypersensitivity reaction of methyldopa, a drug commonly used in the treatment of hypertension, is seroconversion to a positive result of a direct Coombs' test that may lead to a hemolytic anemia. The authors report a case of an infrequently noted, but serious, hypersensitivity reaction to methyldopa, manifesting primarily as acute toxic enterocolitis. A 63-year-old woman was admitted to hospital and underwent aggressive and prolonged investigation of enterocolitis. Withdrawal of methyldopa gave immediate relief of intestinal problems. Rechallenge precipitated a return of symptoms within 14 hours. It is recommended that periodic blood counts and liver function tests be done on patients treated with methyldopa for hypertension. If any abnormalities are noted the drug should be discontinued.

La réaction d'hypersensibilité le mieux connu de la méthyldopa, un médicament couramment utilisé dans le traitement de l'hypertension systolique, est l'induction d'un test direct de Coombs positif, résultat qui peut conduire à une anémie hémolytique. Les auteurs signalent le cas d'une réaction d'hypersensibilité à la méthyldopa, réaction rarement observée mais sérieuse qui se manifeste principalement par une entérocolite toxique aiguë. Une femme de 63 ans, fut hospitalisée pour des examens poussés et prolongés des causes de l'entérocolite. L'arrêt de la méthyldopa a entraîné un soulagement immédiat des problèmes intestinaux. Une nouvelle exposition a précipité le retour des symptômes en moins de 14 heures. Il est recommandé de soumettre les patients traités à la méthyldopa pour hypertension à des numérations cellulaires et à des épreuves fonctionnelles hépatiques périodiques. Si des anomalies sont observées, la médication doit être interrompue.

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Current management regimens for arterial hypertension may include the use of methyldopa, alone or in combination with other antihypertensive medications. The most commonly reported hypersensitivity reaction associated with this drug is seroconversion, giving a positive direct Coombs' test result in 20% of patients, which may lead to hemolytic anemia in 0.02% of cases.[1]

Methyldopa may rarely cause hypersensitivity reactions such as fever, hepatitis, colitis, pancreatitis and myocarditis,[1] reactions that are infrequently noted in standard references and hence can be overlooked. As a result, patients may undergo extensive and unwarranted clinical investigations. We report a case of methyldopa hypersensitivity.

Case Report

A 63-year-old woman was admitted to the general surgical service of the Toronto General Hospital with a provisional diagnosis of acute enterocolitis. She had been receiving antihypertensive (nadolol) and thyroid supplement (L-thyroxine) medications until 1 month before admission with no adverse effects. Because of an upper respiratory tract infection, erythromycin ethylsuccinate was prescribed. Bronchospasm became an increasing problem, necessitating sustained-release theophylline (200 mg twice daily) and methyldopa (250 mg twice daily) and withdrawal of the nadolol. The patient's respiratory symptoms resolved and the theophylline was discontinued. Two weeks after the first dose of methyldopa, she experienced diarrhea, vomiting, undulating fever, chills and debilitating headaches. These symptoms persisted for 10 days and she returned to the hospital. On readmission her vital signs were within normal limits, except for mild pyrexia (38°C orally). There was generalized abdominal tenderness but no other evident abnormalities. Notable laboratory findings included eosinophilia 0.17 $\times 10^9$/L (normal 0.01 to 0.06 $\times 10^9$/L) and an increased alkaline phosphatase level of 118 U/L (normal less than 80 U/L). Standard abdominal x-ray films revealed a large amount of air scattered throughout the intestinal tract, compatible with a diagnosis of paralytic ileus. Appropriate stool cultures grew no important pathogens. In particular there was no *Clostridium difficile* toxin. Proctosigmoidoscopy, abdominal ultrasonography and barium enema examinations gave normal results. In hospital, the patient continued to have undulating fever with a body temperature reaching 40°C, chills, persistent vomiting and diarrhea. Because of a transient drop in her blood pressure, below 100 mm Hg systolic, methyldopa was withheld. For the first time since admission her chills and fever abated. The methyldopa was discontinued with subsequent resolution of the nausea and diarrhea. After 5 days the patient enjoyed good health. We were suspicious of a drug reaction so a test dose (250 mg) of methyldopa was administered to the patient, with a return of acute nausea, chills, fever and abdominal discomfort within 14 hours. She was discharged, free of symptoms, on hospital day 14.

Discussion

Fever with methyldopa has been reported to occur in approximately 3% of patients receiving the drug.[1] It usually develops within the first 3 weeks of therapy, and in some cases is associated with eosinophilia and abnormal results of one or more liver function tests (e.g., serum alkaline phosphatase, serum transaminases, bilirubin and prothrombin time).[2] Our patient demonstrated fever and liver function abnormalities in addition to a pronounced eosinophilia.

There are reports of methyldopa causing colitis and prolonged diarrhea, but fever has not been noted in

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these cases.[3,4] An extensive review[5] from the Swedish Adverse Reaction Reporting Program in 1978 summarized reactions to methyldopa reported over a 10-year period. In this review, 159 patients had a fever; of these, 13 had moderately elevated serum transaminase levels, 8 skin manifestations, 4 gastrointestinal complaints and 2 had eosinophilia. Gastrointestinal symptoms were reported in another 17 patients, diarrhea being the most common complaint. The onset of fever within 3 weeks of drug administration was also noted. The temperatures were high and returned to normal within a couple of days of discontinuing methyldopa therapy. Several patients underwent provocative tests and fever developed within 12 hours of drug administration.[5] Our patient demonstrated a combination of these clinical events. She was also challenged with the drug and her symptoms recurred within 14 hours.

The occurrence of serious adverse reactions with methyldopa is low, but they may cause serious morbidity, unwarranted investigations and result in hospitalization. Rapid recovery after drug withdrawal is the rule, although deaths have been reported due to severe hemolysis or liver failure.

When methyldopa is used to treat hypertension, periodic blood counts and liver function testing are mandatory. If jaundice or abnormalities of liver function are noted, the drug should be discontinued. The onset of fever and enterocolitis within 3 weeks of initiation of methyldopa therapy should alert the physician to the possibility of an adverse drug reaction.

We thank Mr. John K. Murdoch, B Sc(Phm), Drug Information Services, Toronto General Hospital, for his help in researching and preparing the background on adverse drug reactions.

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SESAP V Question

112. Overwhelming sepsis after splenectomy has been recognized since 1952. Which of the following statements about this phenomenon is NOT true?

(A) Progression from onset to death may occur in a matter of hours

(B) Most fatal episodes occur less than two years after splenectomy

(C) *Pneumococci* have been isolated in approximately 50% of the fatal cases.

(D) Patients who have had their spleen removed for hematologic disease have a greater risk for overwhelming sepsis than those who have splenectomy for trauma

(E) Postsplenectomy sepsis has not been reported in patients with splenosis or accessory spleens

For the critique of Item 112 see page 194.

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Primary Resection and Anastomosis of Lesions Obstructing the Left Colon

It is becoming apparent that primary resection and anastomosis of the left colon for colonic obstruction is a feasible operation.

This paper reviews 750 colonic resections at the Queen Elizabeth Hospital of Montreal, of which 40 were performed on unprepared bowel in patients with obstructed left colonic lesions.

The pre- and postoperative hospital stay was greatly reduced. The death rate was 5% and complication rate 40%. Follow-up results suggest this procedure is safe and that an adequate cancer operation can be carried out. It should be stressed that not all obstructing left colonic lesions can be treated with a one-stage procedure and that the Hartmann procedure or a protective colostomy can always be used if the situation warrants it.

Dans les cas d'obstruction colique, il semble maintenant possible de pratiquer une résection primaire et une anastomose du côlon gauche.

Cet article passe en revue 750 résections coliques qui ont été pratiquées à l'Hôpital Reine Elizabeth de Montréal. De ce nombre, 40 cas ont été effectués sur des intestins non préparés, chez des patients souffrant d'une obstruction colique gauche.

Le séjour hospitalier pré et post-opératoire a été grandement réduit. La mortalité fut de 5% et le taux de complications de 40%. Les contrôles ultérieurs indiquent que cette intervention est sûre et qu'elle permet de réaliser une chirurgie anticancéreuse satisfaisante. On doit souligner qu'une intervention en un seul temps ne peut pas être réalisée dans tous les cas d'obstruction colique gauche et qu'une opération de Hartmann ou une colostomie de protection peuvent toujours être utilisées quand la situation l'exige.

The treatment of left colonic lesions by a staged procedure is tedious and time-consuming. Moreover, the 5-year survival rate[1] is very low (16%). Treatment by extended right hemicolectomy,[2] subtotal colectomy or total colectomy[3,4] is radical, the procedures requiring considerable skill and resection of a great deal of normal colon in most cases. The argument that the terminal ileum has a richer blood supply than the colon may be true, but results still show that a considerable number of leaks occur. Fielding and Wells[5] reported that patients with primary resection had a higher 5-year survival than those with staged resections.

In the 6 years 1981 to 1986, 750 colonic resections were performed at the Queen Elizabeth Hospital in Montreal. Of these, 40 were emergency primary resections with anastomosis for obstruction or ruptures of the left colon. It should be noted that not every case was treated this way; in 12 cases the Hartmann procedure[6] was used and in 8 others a protective colostomy was performed when the anastomosis or some other condition made this seem more prudent.

Indications and Contraindications

We believe that all patients with obstructive lesions of the left colon should be considered possible candidates for primary resection and anastomosis with the following exceptions:

- Those with systemic disease.
  (a) Severe medical disease that would not allow a further 45 minutes of surgery.
  (b) Prolonged steroid therapy.
  (c) Inflammatory bowel disease.
- Those with local problems in the pelvis and sigmoid colon that preclude mobilization of the rectum and sigmoid.
  (a) Diffuse metastases in pelvis.
  (b) Phlegmonous diverticulitis.
  (c) Previous radiotherapy.
  (d) Ischemic changes of bowel.
  (e) Necrotic sigmoid volvulus.

Patients

This series consisted of 40 patients (26 women, 14 men) between the ages of 34 and 93 years (average 67.9 years) (Table I).

Of the 40 patients, 30 had carcinoma, 9 diverticulitis and 1 necrotic volvulus of the sigmoid. In three cases there were associated perforations and in two an abscess was present. The stages of the 30 carcinomas were 14 Dukes' B, 8 Dukes' C and 8 Dukes' D.

Preoperative Assessment

In addition to nasogastric suction and intravenous therapy, appropriate preoperative x-ray films were obtained and laboratory investigations carried out. The lower rectum was emptied by gentle enemas and the colon assessed either using a flexible sigmoidoscope or by colonoscopy to confirm the level of the lesion and to obtain a biopsy if possible. Barium

Table I—Age of the 40 Patients in the Study

Age, yr	No.
30 – 40	1
41 – 50	5
51 – 60	8
61 – 70	12
71 – 80	9
81 – 90	4
91 – 100	1

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enema examination was done only if the diagnosis could not be made by colonoscopy. Most patients were taken to the operating room within 48 hours of admission.

Many antibiotics were used perioperatively in the early cases, including combinations of gentamicin, clindamycin, Flagyl and tobramycin. The last 16 patients were given cefoxitin (2 g intravenously on call to the operating room and then postoperatively every 6 hours for 5 days) and this has proved satisfactory.

Operative Technique

Under general anesthesia, the patient is placed in a modified lithotomy position and the rectum examined to make sure it is clean and empty. If fluid is present a rectal tube is put in place.

The appropriate segment of colon containing the lesion is mobilized. The colon distal to the tumour is then transected and a swab placed in the lumen to prevent leakage. A large rectal tube is inserted through a double pursestring suture placed in the proximal distended colon close to the tumour and attached to suction. Copious amounts of normal saline are used to empty the proximal bowel as much as possible. The distended colon above the tumour is milked proximally with the fingers. When the resection area is empty, pressure is applied by the thumb and index finger to occlude the fragile bowel. A clamp is then placed across the colon just proximal to the double pursestring suture holding the rectal tube. The anterior surface of the colon is opened proximal to the clamp and Gelfoam rapidly packed into the lumen to avoid any spillage. We have found this most effective in keeping the anastomotic area clean. The decompressed proximal lumen is then anastomosed to the distal lumen. If any doubt exists as to the integrity of the anastomosis, the peritoneal cavity can be flooded with saline and the rectum distended with air using a bulb syringe. The Gelfoam will obstruct the lumen proximal to the anastomosis to allow good assessment of any air leak. The Gelfoam passes with the first bowel movement. Before abdominal closure, the peritoneal cavity is irrigated with large quantities of normal saline until clean. The abdomen is usually closed without drainage but if a Hemovac drain is necessary it is removed within 48 hours. Skin closure depends upon the extent of contamination, but usually it is wise to leave the skin open, with sutures placed ready for closure later. A single gauze pad soaked in 3% saline is placed in the open wound.

In 20 patients whose wound was closed primarily, 3 had wound infections. In 20 others the wound was left open and closed 5 days postoperatively with no infection.

The mean operating time was 109 minutes.

Table II—Complications

Complication	No.
Urinary obstruction or infection	4
Wound infection	3
Atelectasis or pneumonia	3
Small-bowel obstruction	2
Wound dehiscence	1
Myocardial infarction	1
Deep-vein thrombosis	1
Renal failure	1

Postoperative Care

All patients were managed by nasogastric suction, intravenous administration of fluids, sedation and Foley catheterization. They were kept in the intensive care unit on average for 48 hours. Antibiotic coverage with cefoxitin, 2 g intravenously every 6 hours for 5 days, gave excellent results. The wound was cleansed with 3% saline three times daily, and moist gauze was left in the open wound. Patients were mobilized as rapidly as possible. The Foley catheter on average was removed between day 2 and day 5, depending on the patient's condition.

Wound closure was usually on day 5 and the patient was discharged home on day 7 or 8 if there were no complications. The mean postoperative stay in our series was 14.6 days.

Extent of Resection

Of our 40 patients 6 underwent left hemicolectomy, 26 sigmoid resection, 6 rectosigmoid resection (below 18 cm) and 2 subtotal colectomy. One subtotal colectomy was for a synchronous carcinoma of the cecum and obstructing sigmoid lesion. On sigmoidoscopy, this patient was noted to have a polyp in the rectum, and we thought subtotal colectomy was the appropriate treatment. The second case was an obstructing carcinoma of the sigmoid with perforation of the cecum.

Complications (Table II)

There were two deaths. An 84-year-old man suffered a myocardial infarction on postoperative day 7, followed by renal failure, and he died on day 11. The second was a weak, senile, 89-year-old man who had necrotic volvulus of the sigmoid. A wound infection, dehiscence and pneumonia developed and he died when treatment was withdrawn at his family's request.

Of the other complications, the four cases of urinary obstruction or infection probably occurred because the Foley catheter was withdrawn too soon in these elderly men. The two patients with small-bowel obstruction both required surgery. Of note is that five of the complications occurred in the two patients who died.

Comments

Disparate diameter of bowel lumen was not a problem in our series as the lumen rapidly returns to reasonable dimensions following decompression and irrigation of the bowel. Necrotic sigmoid volvulus is associated with a very poor result in our hands and requires further assessment.

From our study it would seem that in patients with lesions obstructing the left colon, resection with primary anastomosis can be performed with a reasonable death rate of 5%. Many of these patients are elderly and would have a hard time enduring two or three procedures. The morbidity of 40% could be lowered by leaving all wounds open. Cefoxitin is satisfactory for controlling sepsis. Gelfoam packed in the proximal lumen will avoid spillage in the obstructed colon after decompression by irrigation. The Gelfoam passes through the anastomosis with little problem. However, not all cases of left colonic obstruction are suitable for a one-stage operation, and the Hartmann procedure or a protective colostomy are still sometimes indicated.

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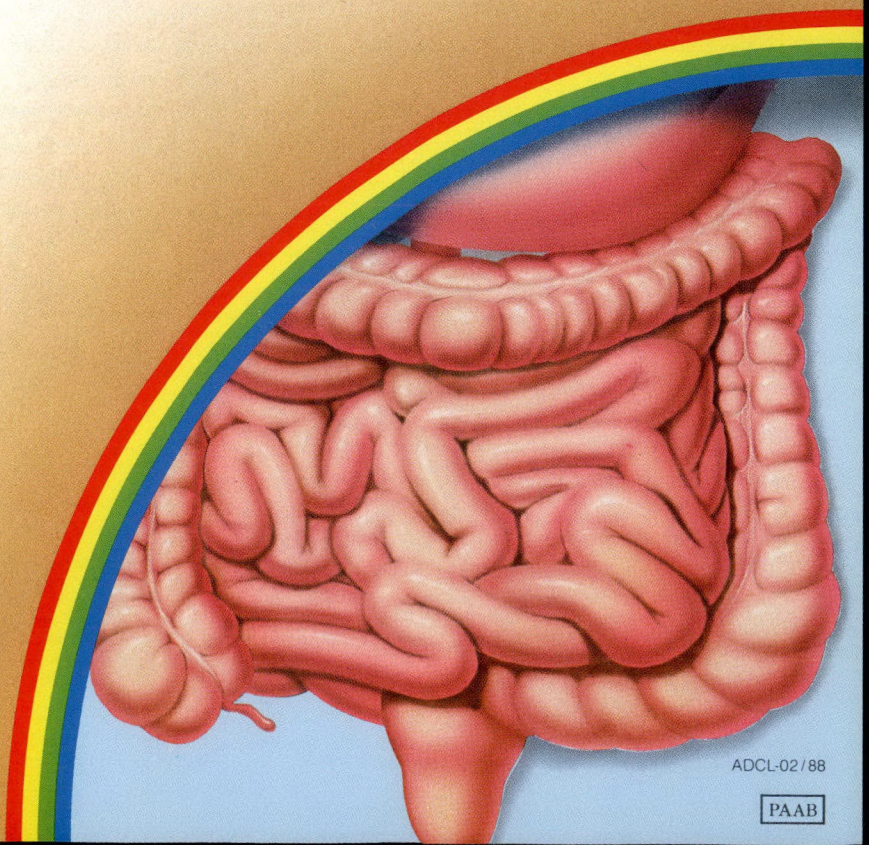

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In vitro studies indicate that the bacterial action of CLAFORAN (cefotaxime sodium) a semi-synthetic cephalosporin antibiotic, results from inhibition of cell wall synthesis.

Indications and Clinical Uses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Contraindications

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

Warnings

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

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

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

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

Precautions

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

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

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

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

Prolonged use of CLAFORAN may result in the overgrowth of nonsusceptible organisms. Constant evaluation of the patient's condition is essential. If superinfection occurs, therapy should be discontinued and appropriate measures taken.

Although CLAFORAN rarely produces alterations in kidney function, evaluation of renal status is recommended, especially in severely ill patients receiving high doses.

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

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

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

Adverse Reactions

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

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

Symptoms and Treatment of Overdosage

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

Dosage and Administration

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

Dosage

Adults

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

Guidelines for Dosage of CLAFORAN (cefotaxime sodium)

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

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

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

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

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

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

Caesarian Section Patients

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

Neonates, Infants, and Children

The following dosage schedule is recommended :

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

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

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

The maximum daily dosage should not exceed 12 grams.

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

Dosage for Patients with Impaired Renal Function

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

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

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

Administration

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

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

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

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Reconstitution

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

Reconstitution Table

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

*shake to dissolve.

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

Reconstitution Table

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

*shake to dissolve.

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

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

CLAFORAN is also compatible with lignocaine 1%.

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

Stability of Solution

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

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

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

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

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

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

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

Availability

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

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

Product monograph available on request

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Treatment of Experimental Peritonitis With Intraperitoneal Povidone-Iodine Solution

Intraperitoneal lavage with povidone-iodine solution has been reported by some to be beneficial in the treatment of peritonitis and by others to cause local and toxic side effects. In this study, 200 white mice, divided into four groups of 50, were subjected to bacterial peritonitis. The first group had no treatment; peritoneal lavage was carried out using povidone-iodine solution in the second group and a 0.9% sodium chloride solution in the third. In the fourth group, antibiotics (clindamycin and gentamicin) were instilled intraperitoneally without peritoneal lavage. The povidone-iodine solution had no beneficial effect, the death rate after 1 week (76%) being similar to that in the control group (78%) and much higher than that in mice treated with sodium chloride lavage (38%) and antibiotics without lavage (16%). A second series of experiments was, therefore, carried out to investigate the toxic effect of povidone-iodine solution intraperitoneally on mice without peritonitis; the solution was found to be toxic.

Il a été rapporté par certains que le lavage intrapéritonéal à la povidone-iode pouvait être utile dans le traitement de la péritonite alors que d'autres ont signalé des réactions locales et des réactions indésirables toxiques. Dans cette étude, on a provoqué une péritonite bactérienne chez 200 souris blanches réparties en quatre groupes de 50. Le premier groupe n'a reçu aucun traitement; le second groupe a été soumis à un lavage de plèvre à la povidone-iode, alors que le troisième groupe recevait un lavage au chlorure de sodium à 0.9%. Chez le quatrième groupe, des antibiotiques (clindamycine et gentamicine) ont été instillés dans la cavité péritonéale, mais il n'y a pas eu de lavage de plèvre. La solution de povidone-iode n'a exercé aucun effet bénéfique, la mortalité après 1 semaine (76%) étant similaire à celle du groupe témoin (78%) et beaucoup plus élevée que chez les souris ayant reçu un lavage au chlorure de sodium (38%) ou des antibiotiques sans lavage (16%). Une deuxième série d'expériences a donc été démarrée pour étudier la toxicité de la povidone-iode en lavage intrapéritonéal chez des souris qui n'avaient pas de péritonite. La solution s'est avérée toxique.

Peritonitis is responsible for approximately 50% of the deaths from septic shock. As a treatment for peritonitis, lavage of the peritoneal cavity with antiseptic and antibacterial solutions gives good results.[1,2] No clear benefit has been documented from lavage with povidone-iodine solution.[1-11] Recently, this solution has been used preoperatively in elective colonic surgery,[3,5] in the treatment of fungal[12] and other infections of the skin[13] and in the treatment of burns,[14] and has been found useful.

We carried out a two-stage experiment, first to find out if povidone-iodine solution was of benefit as a lavage fluid in the treatment of peritonitis and second to study its toxicity in this context.

Materials and Methods

Stage 1

Two hundred white mice of both sexes (mean weight 35 g) were injected intraperitoneally with 0.2 ml of *Escherichia coli* solution.

They were divided into four groups of 50 each: group 1 control, group 2 povidone-iodine lavage, group 3 sodium chloride lavage, group 4 antibiotics but no lavage.

With the exception of group 4, each animal was anesthetized with ether and subjected to laparotomy 6 hours after bacterial injection.

Group 1. — Only peritoneal biopsies and cultures were performed.

Group 2. — In addition to biopsies and cultures the peritoneal cavities were lavaged with povidone-iodine diluted to 1 in 20 with Ringer's lactate solution. After lavage, fluid was again taken from the peritoneal cavity for culture.

Group 3. — The same procedures as in group 2 were followed using sodium chloride (0.9%) as the lavage solution.

Group 4. — No laparotomy was performed on these 50 mice. They were treated with 40 mg/kg clindamycin and 8 mg/kg gentamicin divided into two equal doses over 24 hours.

The mice were followed up for 2 weeks. When one died, its peritoneal cavity was cultured and biopsies were taken from the liver, mesentery and small intestine. All biopsies were examined under the light microscope.

Stage 2

Twenty healthy mice were subjected to laparotomy and their peritoneal cavities lavaged with the povidone-iodine solution. As a control group, another 20 mice were subjected to laparotomy but not lavaged. Iodide concentrations in the blood, liver and peritoneum were measured on postoperative days 1 and 2 with a potentiometer.

Statistical Analysis

The χ^2 test was used to calculate statistical differences; p values less than 0.05 were considered significant.

Findings

Stage 1

In the mice subjected to laparotomy *E. coli* was identified in all cultures

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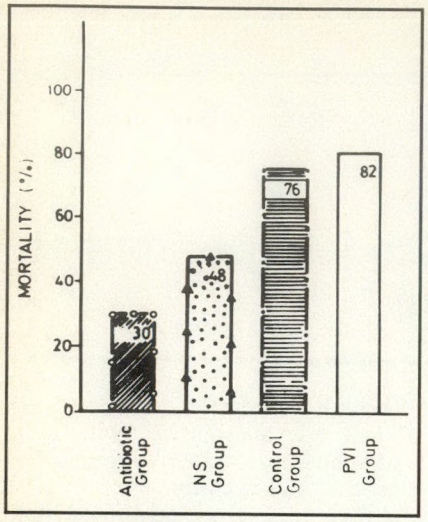

FIG. 1 — Mortality in mice with peritonitis after 2 weeks. NS = sodium chloride, PVI = povidone-iodine.

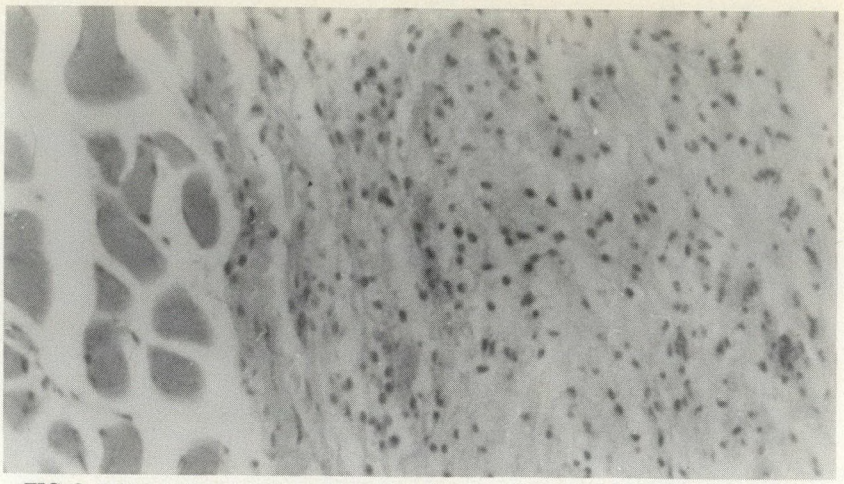

FIG. 2 — Necrosis and inflammation in peritoneum (hematoxylin and eosin, × 100).

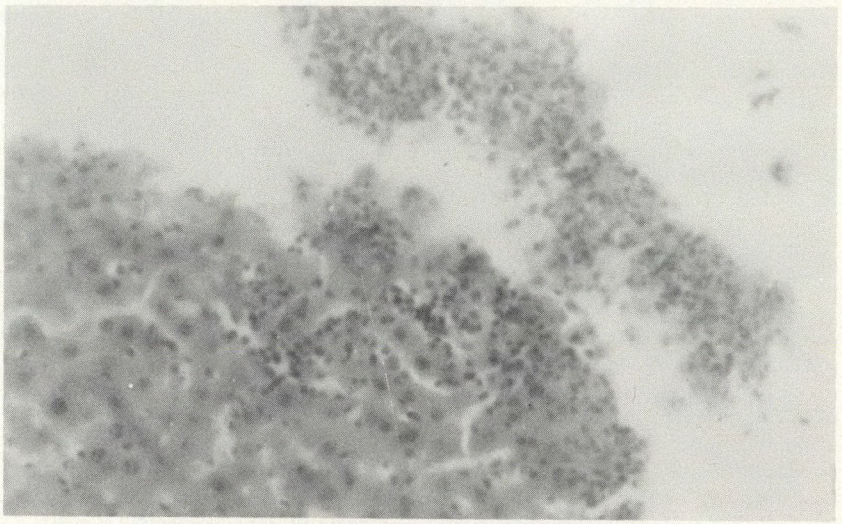

FIG. 3 — Inflammatory cell infiltration in liver (hematoxylin and eosin, × 100).

taken and in addition to reactionary ascites the viscera and peritoneum were hyperemic.

Necrosis and inflammation (rich in neutrophils, poor in lymphocytes) were seen in peritoneal biopsies (Fig. 1).

At the end of 1 week, the death rates in groups 1 to 4 were 78%, 76%, 38% and 16% respectively. Similar results were noted at the end of week 2 (Fig. 2). The povidone-iodine solution had no positive effect whereas sodium chloride solution and antibiotics did. Also, the death rate for group 2 mice was higher than that of the group 1 control. The difference between these two groups was not significant, but the difference between group 1 and other groups was.

Cultures from the peritoneal cavities of mice that died grew *E. coli* and the liver, small bowel and mesenteric biopsies showed inflammatory cells (Figs. 3 to 5).

Stage 2

The death rates in the lavage group were 40% on day 1 and 45% on day 2 compared with only 10% for both days in the control group ($p < 0.05$) and did not change during a 1-week observation period.

At the end of day 1 iodine values had increased twofold in blood and approximately sevenfold in the liver and peritoneum of mice lavaged with the povidone-iodine solution. These values returned to normal by the end of day 2 (Fig. 6).

Discussion

Identification of the source and type of bacterial and chemical contamination is of prime importance in the treatment of peritonitis.[1] The systemic administration of antibiotics, fluid and electrolytes, decompression of the gastrointestinal system and peritoneal lavage with antibiotics and antibacterial agents are also recommended.[1,2,6,11]

The use of the povidone-iodine solution as a peritoneal lavage fluid is still debatable; some recommend it, others condemn its use because of its local and toxic side effects.[1-7,15-18]

Gilmore and colleagues[2,5,6] reported that povidone-iodine solution yielded good results with no toxicity in both their clinical and experimental studies. Other reports noted that lavage with povidone-iodine decreased the number of deaths, reduced wound infection and had no side effects, especially in the treatment of fecal and purulent peritonitis.[7,9,12] It is still used in the treatment of burn patients.[14]

McAvinchey and colleagues[19] in their study using peritoneal irrigation in the treatment of peritonitis in rats found the death rates were 90%, 60% and 0% in the povidone-iodine, control and metronidazole plus amikacin sulfate groups respectively. In the first stage of our study, at the end of week 1 the death rates were 78% in the povidone-iodine group, 76% in the control group, 38% in the sodium chloride and 16% in the antibiotic groups. One week later these rates were 82%, 76%, 48% and 30% respectively. Consequently, it can be said that the povidone-iodine solution had no beneficial effect in our study.

Ahrenholz[1] found that povidone-iodine lavage caused chemical burns in the peritoneal cavity and had a toxic effect not only on bacteria but also on peritoneal cells.

Lineaweaver and colleagues[20] investigated the effects of 1% povidone-iodine, 0.25% acetic acid, 3% hydrogen peroxide and 9.5% sodium hypochlorite on wound healing. They found that all these solutions exerted

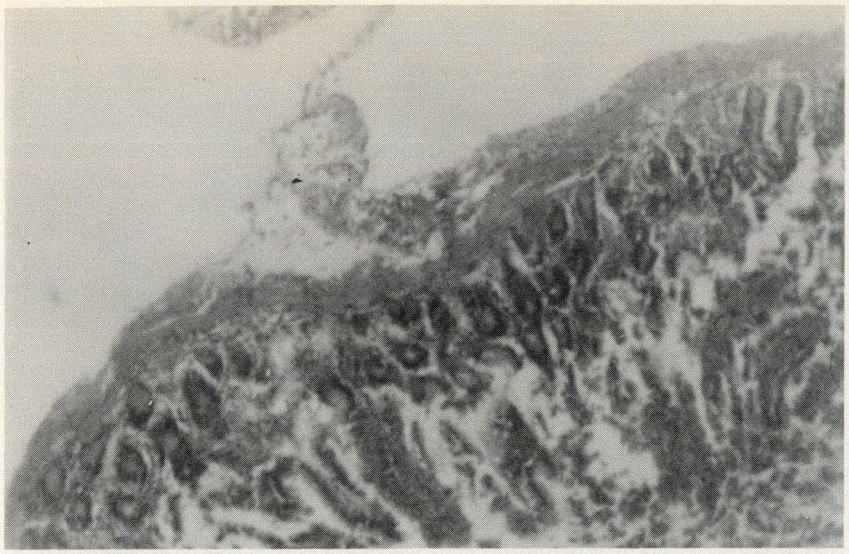

FIG. 4 — Inflammatory cells in intestine (hematoxylin and eosin, × 40).

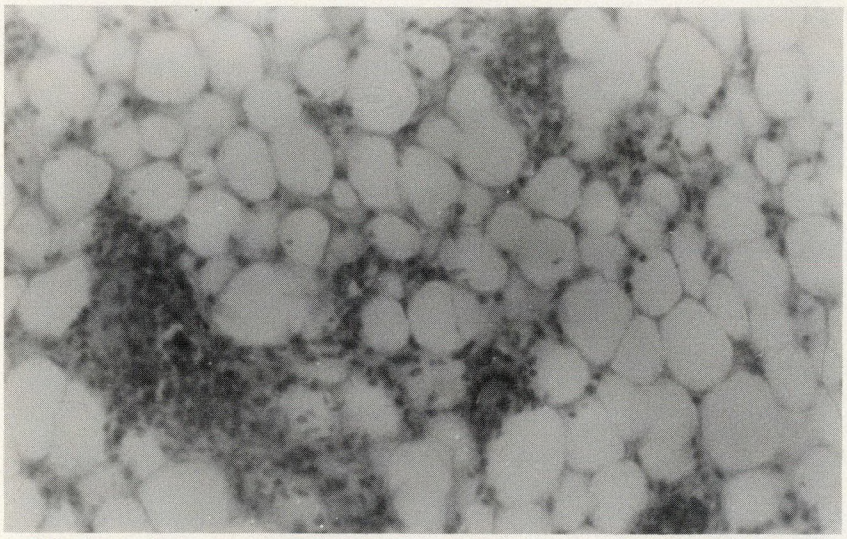

FIG. 5 — Inflammatory cell infiltration in mesentery (hematoxylin and eosin, × 100).

toxic effects on fibroblasts (povidone-iodine caused a 25% to 30% cell death).

Mathews and colleagues[18] investigated various concentrations of povidone-iodine in the treatment of fecal peritonitis in rats, using 0.1%, 0.5%, 1.0% and 5.0% solutions and reported death rates of 66%, 22%, 78% and 100% respectively. They also found an 83% death rate with normal saline solution. These findings are comparable to ours. They also stated that as the number of abdominal lavages with iodine solution increased, so did the number of deaths.

In the second stage of our study, mice lavaged with povidone-iodine solution displayed a twofold iodide concentration in the blood and a sevenfold increase in the peritoneum and the liver on postoperative day 1.

Sindelar and colleagues,[8] using the povidone-iodine solution as a peritoneal lavage fluid, found that the blood iodide concentrations showed a ninefold increase in 24 hours.

In our experiment the death rates were high in mice with or without peritonitis, when they were treated with the povidone-iodine solution. We believe this was due to toxic side effects; the maximal iodide concentrations in the various tissues during the first 2 days, when death rates were the highest, supports this view.

From our findings in this experiment, we conclude that povidone-iodine solution is not recommended in the treatment of bacterial peritonitis because of its toxicity and associated high death rates.

We thank Sedat Torel for his assistance in the English translation of this paper.

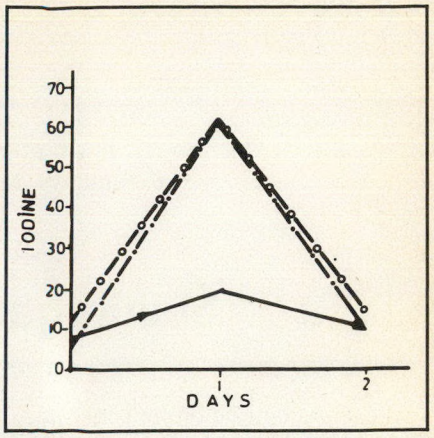

FIG. 6 — Iodide concentrations (ng/ml) in blood (———), peritoneum (—•—•—) and liver (o—o—o).

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Multiorgan Failure in Critically Ill Patients

Of 1136 patients admitted consecutively to two medical-surgical intensive care units, 100 were found to have multiorgan failure, defined as failure of more than two organ systems. The average duration of stay in the intensive care units was 13.4 days. The overall death rate was 78% compared with 12.8% for patients without multiorgan failure. The most common initiating illnesses or insults were sepsis, surgery, accidental trauma and cardiogenic shock. Of potential risk factors studied, shock, sepsis, surgery, pre-existing organ disease and age over 65 years were the most common. Although sepsis occurred before or during the course of multiorgan failure in 78 patients, in only 34 was sepsis judged to be the prime insult leading to multiorgan failure. Surgery during the course of multiorgan failure had neither an adverse nor beneficial effect on outcome. The mean number of organ systems failing was 4.36 for survivors and 5.03 for nonsurvivors. The most common systems to fail were central nervous, cardiovascular and respiratory.

Sur 1136 hospitalisations consécutives à deux unités de soins intensifs médico-chirurgicaux, 100 patients souffraient d'une défaillance plurifonctionnelle définie comme l'insuffisance de plus de deux organes. La durée moyenne du séjour aux soins intensifs a été de 13.4 jours. La mortalité globale fut de 78% comparativement à 12.8% pour les patients qui n'étaient pas atteints de défaillance plurifonctionnelle. Les maladies ou lésions causales les plus fréquentes étaient la sepsie, la chirurgie, les traumatismes et le choc cardiogénique. Parmi les facteurs de risque étudiés, le choc, la sepsie, la chirurgie, une maladie organique préexistante et un âge supérieur à 65 ans ont été le plus souvent retrouvés. Même si une sepsie est survenue avant ou durant une défaillance plurifonctionnelle chez 78 patients, on juge qu'elle fut la principale cause de cette défaillance dans seulement 34 cas. La chirurgie pendant une période de défaillance plurifonctionnelle paraît n'avoir eu ni influence bénéfique, ni effet indésirable sur l'issue. Le nombre moyen d'organes défaillants fut de 4.36 pour les survivants et de 5.03 pour ceux qui sont décédés. Les systèmes les plus souvent touchés ont été les systèmes nerveux central, cardiovasculaire et respiratoire.

Many patients with serious illnesses, previously the cause of death, are now cured by modern intensive care techniques. The course of critical illness is frequently dictated by the multiorgan failure syndrome (MOFS), which may be defined as dysfunction of more than two organ systems.[1] It is associated with a high death rate, indicating that current methods of treatment are inadequate.

Previous studies[2-6] have identified risk factors that influence the development and outcome of MOFS after a common insult, such as sepsis. This report examines a group of patients with multiorgan failure after a variety of insults, to determine its prevalence, initiating factors and prognostic significance in critically ill patients in medical-surgical intensive care units, whether there are causative factors, such as sepsis, that are common to all patients with multiorgan failure and whether appropriate surgical intervention affected survival.

Patients and Methods

The charts of all patients admitted over a 1-year period to the combined medical-surgical intensive care units at University and Victoria hospitals, London, Ont., were reviewed. Those with failure of more than two organ systems are the subject of this study.

The patients were divided into "surgery" and "no surgery" groups. All patients in the surgery group had a surgical procedure under general anesthesia either immediately before or during MOFS. The "no surgery" group had no operative procedure either before or during MOFS.

The criteria for organ failure are in agreement with those used in other studies.[1-5,7]

Pulmonary failure was defined by: a fall in arterial oxygen tension to less than 50 mm Hg on room air, the need for mechanical ventilation for longer than 48 hours because of hypoxemia or hypoventilation, or radiologic evidence of pulmonary edema with a pulmonary capillary wedge pressure of less than 18 mm Hg.

Cardiovascular failure was defined by a cardiac index of less than 2.5 $L/min \cdot m^{-2}$ with normal or elevated filling pressures, or dependence on inotropic drugs to maintain adequate tissue perfusion as assessed by clinical criteria.

Renal failure was indicated by a serum creatinine level of more than 176.8 μmol/L, or double the previous level if pre-existing renal impairment was present, or a creatinine clearance of less than 0.5 ml/s or urine output less than 30 ml/h over 24 hours, despite adequate hydration.

Liver failure was defined as a rise in the serum bilirubin level of more than 68.4 μmol/L or the aspartate aminotransferase to more than twice the normal level in the absence of duct obstruction, hemolysis or hepatitis of viral or toxic etiology.

The criteria for failure of the hemopoietic system were a platelet count of less than 50×10^9/L in the absence of previously documented autoimmune thrombocytopenia, disseminated intravascular coagulation documented by fibrinogen levels of less than 2.0 g/L, fibrin-fibrinogen degradation products greater than 10 μg/ml or positive protamine sulfate test, or a

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clinical bleeding diathesis as indicated by spontaneous bleeding from mucous membranes or bleeding from puncture sites.

Gastrointestinal failure was defined by a patient's inability to tolerate enteral feeding in the absence of mechanical obstruction and excluding an initial 5-day period after abdominal surgery, acalculous cholecystitis, pancreatitis in the absence of gallstones, trauma or alcohol abuse, or gastrointestinal bleeding requiring transfusion of more than two units of packed cells in 24 hours.

Central nervous system failure was a decreased level of consciousness ranging from confusion to coma in the absence of CNS infection or structural abnormalities.

The initiating illness or insult is defined as the single most important life-threatening illness from which the patient did not recover before the onset of MOFS.

In our study, risk factors are classed as those that might influence survival of MOFS patients; they differ from initiating factors. Some could not by themselves cause MOFS (e.g., smoking, low serum albumin level) but would have been present before its onset; others occurred after the onset of MOFS. For each patient the following potential risk factors were recorded: age greater than 65 years, obesity, malnutrition, diabetes mellitus, malignant disease, alcohol abuse, smoking, immune suppression, shock, sepsis, surgery, gastrointestinal bleeding and pre-existing organ dysfunction.

We defined malnutrition as a serum albumin level less than 25 g/L, weight loss of more than 10% within 30 days or more than 20% within 6 months, weight more than 20% below the ideal body weight or energy intake of less than 4184 kJ/d for 7 days or more.[3]

Criteria for immune suppression included: continuous steroid therapy for longer than 30 days, high-dose steroid therapy of more than 15 mg/kg of methylprednisolone or its equivalent for 5 days or longer, chemotherapy within 1 year, radiotherapy within 1 year, lymphoma or immune deficiency syndrome.[3]

Shock was defined by a systolic blood pressure of less than 80 mm Hg for longer than 30 minutes.

Sepsis was indicated by: the presence of appropriate organisms on culture supported by clinical signs of fever, leukocytosis and physical or radiologic findings, including findings at laparotomy (abscess, necrotic bowel, perforation of a hollow viscus and peritonitis). Pre-existing organ dysfunction was indicated by angina pectoris, previous myocardial infarction, congestive heart failure, chronic obstructive lung disease, chronic renal failure or biopsy proven cirrhosis.

Mean values of variables were compared by unpaired *t*-tests. Differences were considered significant at a p value of < 0.05.

Findings

Incidence

Of 1136 critically ill patients admitted consecutively to the two medical-surgical intensive care units, 100 (8.8%) had MOFS. There were 67 males and 33 females ranging in age from 6 to 84 years (mean 61.4 years). There was no significant difference in age between survivors and nonsurvivors. The average duration of stay in the intensive care units was 13.4 days (range from 1 to 78 days). Survivors spent a mean of 20 days in the intensive care unit and nonsurvivors a mean of 12 days ($p < 0.0005$). The death rate, when there was failure of three or more organ systems, was 78% versus 12.8% in patients without MOFS.

Initiating Illness or Insult

The primary insult or initiating event for the MOFS was most commonly sepsis, followed by surgery, accidental injury and cardiogenic shock (Table I). When serious sepsis occurred with another insult it was arbitrarily considered to be the initiating illness.

Time Sequences

There was no significant difference in the time interval between the primary insult and the onset of MOFS between the survivors and nonsurvivors (4.4 ± 5.4 days versus 6.6 ± 9.9 days respectively) ($p = 7.05$). Patients who died within 24 hours of the primary insult were excluded from the study.

The interval between primary insult and death was 26.5 ± 25.8 days and 8.5 ± 6.3 days for the surgical and nonsurgical groups respectively ($p < 0.001$).

In 45%, MOFS began within 24 hours of the initial insult; in 11% of patients MOFS developed more than 2 weeks after the initial insult.

The interval between the primary insult and death in both groups manifested a distinct trend. In the nonsurgical group, 38% died within 5 days after which there was a gradual decrease in the number of deaths. In the surgical group there were two peaks: early, within 5 days of the initial insult, and late, after 2 weeks. This includes 30% who died more than 4 weeks after their initial insult.

The majority of patients died within 5 days of the development of MOFS. In the nonsurgical group there were no deaths after 2 weeks.

Risk Factors

The frequency of potential risk factors is shown in Table II. Shock, sepsis, surgery, pre-existing organ disease and age greater than 65 years were most common, in decreasing order of frequency. Comparison of survivors and nonsurvivors using χ^2 analysis showed that malnutrition and malignant disease were more common in nonsurvivors ($p < 0.05$).

Episodes of hypotension were doc-

Table I—Primary Insult

Insult	Surgery, no. (%)		No surgery, no. (%)		Totals
	Nonsurvivors (n = 43)	Survivors (n = 17)	Nonsurvivors (n = 35)	Survivors (n = 5)	
Sepsis	11 (26)	5 (29)	17 (49)	1 (20)	34
Surgery	18 (42)	5 (29)	0	0	23
Trauma	4 (9)	7 (41)	1 (3)	0	12
Myocardial infarction or heart failure	2 (5)	0	9 (26)	1 (20)	12
Gastrointestinal bleeding	3 (7)	0	4 (11)	1 (20)	8
Hypovolemic shock	3 (7)	0	0	1 (20)	4
Respiratory failure	0	0	1 (3)	1 (20)	2
Pancreatitis	1 (2)	0	0	0	1
Malignant disease	0	0	1 (3)	0	1

umented in 90% of patients, making it the most common risk factor for multiorgan failure. Septic and cardiogenic shock were the most frequent causes of hypotension, but hypotensive periods occurred before the development of MOFS in only 76% of patients.

Pre-existing Organ Dysfunction

Pre-existing organ dysfunction was present in 60 of the 100 patients and the affected organ system was first to fail in the course of MOFS in 47% of these cases.

Sepsis

Although sepsis has been widely implicated as the major cause of MOFS,[2,5-7] we found that in only 34 patients was it the initiating event or cause of multiorgan failure. To be considered as the cause of MOFS, sepsis had to occur before the onset of any organ failure. In 78% of patients, sepsis occurred before or during the course of multiorgan failure, its frequency being similar in both surgical and nonsurgical groups.

Of 44 surgical patients who had sepsis, only 22 had the complication before the onset of MOFS. Thus, even in the surgery group sepsis cannot be implicated as a cause in more than 50%. The two most common locations of the septic process were bronchopulmonary and intra-abdominal (Table III). Many patients had more than one focus or more than one episode of sepsis.

Intra-abdominal Sepsis With MOFS

When intra-abdominal sepsis was combined with MOFS the death rate was 84%, and it was 78% ($p > 0.05$) in patients who did not have intra-abdominal sepsis. Twenty-five patients with MOFS had intra-abdominal abscesses; all were drained, 22 operatively and 3 percutaneously. Despite adequate surgical intervention only four of these patients survived.

Blood Cultures and MOFS

Twenty-two of 35 nonsurvivors in the nonsurgical group had positive blood cultures; none of the survivors had positive blood cultures ($p < 0.0005$ [χ^2 analysis]). However, in the surgical group, positive blood cultures were not necessarily associated with poor survival.

Surgery in MOFS

The role of surgery in treatment of MOFS was examined. Of 44 patients who had surgery during the course of MOFS, it was for "cure" (e.g., drainage of abscess) in 26 and for other indications in 18. Comparing the surgical and nonsurgical groups by χ^2 analysis, we found that surgery during the course of MOFS either for "cure" or other indications had neither an adverse nor beneficial effect on outcome. We could not determine the effect of surgery on outcome in the patients for whom surgery was indicated, because surgical treatment was never withheld; thus, there was no control group. Our impressions were that in surviving patients who had surgery for "cure", the intervention tended to be early in the course of the syndrome.

Number of Organ Systems Failing

By entrance criteria, all patients had failure of more than two organ systems. Most patients had failure of four to six organ systems (mean 4.36 for survivors and 5.03 for nonsurvivors) ($p < 0.05$) (Table IV). Cardiovascular and renal failure were more common in nonsurvivors than in survivors ($p < 0.05$).

The most common systems to fail were the central nervous, cardiovascular and respiratory systems (Table IV). The respiratory system was most

Table II—Potential Risk Factors for Multiorgan Failure Syndrome (MOFS)

	Surgery, no. (%)		No surgery, no. (%)				
Risk factor	Nonsurvivors (n = 43)	Survivors (n = 17)	Nonsurvivors (n = 35)	Survivors (n = 5)	Nonsurvivors, no. (%) (n = 78)	Survivors, no. (%) (n = 22)	Totals
Age	22	8	20	4	42 (54)	12 (55)	54
Obesity	9	3	6	1	15 (19)	4 (18)	19
Malnutrition	19	4	17	1	36 (46)	5 (23)	41*
Diabetes mellitus	9	1	4	0	13 (17)	1 (5)	14
Malignant disease	12	1	8	0	22 (28)	1 (5)	23*
Alcohol abuse	11	3	13	2	24 (31)	5 (23)	29
Smoking	16	4	12	1	28 (36)	5 (23)	33
Immune suppression	6	0	4	0	10 (13)	0 (0)	10
Shock	38	15	34	3	72 (92)	18 (82)	90
Sepsis	33	14	26	5	59 (76)	19 (86)	78
Surgery	43	17	0	0	43 (55)	17 (77)	60
Pre-existing organ disease	24	8	23	5	47 (60)	13 (59)	60
Gastrointestinal bleeding	3	1	4	1	7 (9)	2 (9)	9

*$p < 0.05$ survivors versus nonsurvivors.

Table III—Foci of Sepsis

	Surgery, no. (%)		No surgery, no. (%)		
Focus	Nonsurvivors (n = 43)	Survivors (n = 17)	Nonsurvivors (n = 35)	Survivors (n = 5)	Totals
Pulmonary	10 (23)	4 (24)	11 (31)	3 (60)	28
Abdominal	18 (42)	4 (24)	3 (9)	0	25
Blood stream	5 (12)	1 (6)	10 (29)	0	14
Central lines	3 (7)	3 (18)	3 (9)	0	9
Soft tissue/wounds	3 (7)	2 (12)	4 (11)	0	9
Genitourinary	0	3 (18)	1 (3)	4 (80)	8

frequently the first to fail but was followed closely by the other two.

The overall death rate associated with MOFS in patients with more than two organ system failures was 78.0% (Table V), compared with 12.8% for patients in the intensive care unit without MOFS.

Discussion

One would not expect multiorgan failure to be a feature of untreated injury or infection, and it was not described in the past when available treatment for sepsis and injury was minimal. Modern treatment prolongs critical illness and is likely a permissive factor that allows time for multiorgan failure to occur. However, interventions such as operation, anesthetics and analgesics, intubations, restraints and invasive monitoring, may have a causative role.

Tilney and colleagues[8] first described multiple organ failure following treatment of patients who had ruptured abdominal aortic aneurysms. Since then, MOFS has been associated with intra-abdominal infections, accidental trauma and surgical procedures.[2-5] Most authors have described multiorgan failure occurring secondary to one of these initiating factors. To achieve a broader view, we studied multiorgan failure in all admissions to two medical-surgical intensive care units. In this setting, the initiating factors are multiple and include sepsis, accidental trauma, surgical trauma, myocardial infarction, hypovolemic shock, primary respiratory failure, pancreatitis and malignant disease. We did not find a single cause or abnormal state that was common to all patients with multiorgan failure; hypotension came closest as it preceded the syndrome in 78% of cases. It seems clear that multiorgan failure may be initiated by a wide range of illnesses or injuries.

Sepsis

Whereas Fry and colleagues[5] found that 95% of patients with MOFS after emergency laparotomy had sepsis, Faist and colleagues[4] found only 56%. In our series, sepsis was identified in 78 patients but was the initiating event in only 34. None the less, clinical observation suggests that sepsis occurring during MOFS contributes to its progression.

Intra-abdominal sepsis is particularly devastating. It was associated with a death rate of 84% in patients with MOFS, despite appropriate surgical intervention. This high rate has been noted by others.[9,10] Indeed, Fry and colleagues[11] found that organ failure was one of the determinants of death in patients with intra-abdominal abscess.

Sepsis and Surgical Intervention

Some[6,7,10] have suggested that unexplained development or worsening of organ failure is due to intra-abdominal sepsis, which may or may not be evident from clinical signs and localization studies. These authors suggest that "blind" or non-directed laparotomy in such patients may uncover pus and therefore improve survival. In the series of Ferraris,[9] laparotomy in patients with MOFS was associated with a 52% death rate. Other studies report much higher death rates. When non-directed laparotomy was performed as a potentially curative procedure, death rates were as high as 80% and 100%.[10,12] The mortality is also high if no intra-abdominal cause for MOFS is found. Death rates of this magnitude make it difficult to justify blind laparotomy in MOFS. In our series, even when surgery was clearly indicated (laparotomy in this group), directed and positive, the death rate was 84%. We concluded therefore that although laparotomy is reasonable as a directed procedure, it is hard to justify as a non-directed procedure. Others[13] have reached the same conclusion.

Pre-existing Organ Disease

Pre-existing organ disease may be a risk factor for multiorgan failure. Eiseman and associates[14] found that 23 of 42 MOFS patients had pre-existing organ disease and that the diseased organ subsequently failed during the course of multiorgan failure. In our series, 60 patients had pre-existing organ disease and in 28 the diseased organ was the first to fail. However, in 10% of the patients, the diseased organ was not involved in subsequent organ failure.

Etiology of MOFS

There has been much speculation about the underlying etiology of multiorgan failure. Some considered that sepsis was the predominant factor while others have implicated shock. Certainly both are associated with the syndrome. In our series, all patients had either sepsis or shock before the onset of organ failure. Goris and colleagues[15] have suggested that the basic feature common to all patients with MOFS is severe inflammation. They suggest that toxic oxygen radicals released by phagocytes which have been

Table IV—Number of Organ Systems Failing and Associated Death Rates

No. of systems failing	Nonsurvivors (n = 78)	Survivors (n = 22)	Total no.	Death rate, %
3	5	6	11	45
4	24	5	29	83
5	19	9	28	68
6	24	1	25	96
7	6	1	7	86
Mean	5.03	4.36		

Table V—Organ Systems That Failed

	Surgery, no. (%)		No surgery, no. (%)				
Organ system	Nonsurvivors (n = 43)	Survivors (n = 17)	Nonsurvivors (n = 35)	Survivors (n = 5)	Nonsurvivors, no. (%) (n = 78)	Survivors, no. (%) (n = 22)	Totals
Cardiovascular	39	10	31	4	70 (90)	14 (64)	84*
Pulmonary	39	13	29	4	68 (87)	17 (77)	85
Renal	35	8	28	3	63 (81)	11 (50)	74*
Hepatic	27	13	23	1	50 (64)	14 (64)	64
Blood	23	10	22	1	45 (58)	11 (50)	56
Central nervous	35	14	34	3	69 (88)	17 (77)	86
Gastrointestinal	20	12	7	0	27 (35)	12 (55)	39

*$p < 0.05$ survivors versus nonsurvivors.

stimulated as a result of tissue trauma, burns, endotoxin and other agents are responsible for the picture of generalized severe inflammation and remote organ failure. Richards and colleagues[16] have suggested that fibronectin deficiency is associated with multiorgan failure.

Conclusions

Multiorgan failure is common (8.8% incidence) in medical-surgical intensive care units. Its etiology is multifactorial. Sepsis and shock are the most prominent features but are not always present. The death rate in patients with failure of three or more organ systems is 78% compared with 12.8% in critically ill patients without multiorgan failure. Current methods of treatment are inadequate. Surgical intervention is associated with a very high mortality even when pus is found and drained. It is difficult to justify use of blind or non-directed laparotomy.

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MEFOXIN* to pregnant patients is considered necessary, its use requires that the anticipated benefits be weighed against possible hazards to the fetus. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to MEFOXIN*.

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

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

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

ADVERSE REACTIONS

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

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

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

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

Blood
Transient eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia have been reported. Some individuals, particularly those with azotemia, may develop positive direct Coombs tests during therapy with MEFOXIN*.

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

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

TREATMENT OF OVERDOSE

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

DOSAGE AND ADMINISTRATION

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

TREATMENT DOSAGE

Adults

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

Usual Adult Dosage

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

*Including patients in whom bacteremia is absent or unlikely

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

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

Adults with Impaired Renal Function

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

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

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

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

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

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

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

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

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

PROPHYLACTIC USE

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

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Lipomas of the Colon: a Clinicopathologic Review

The authors review their experience with lipomas of the colon at St. Boniface General Hospital in Winnipeg, Man., during the period 1974 to 1985, and compare their clinicopathologic evaluation with that reported in the literature.

Among 15 patients (average age 66.7 years), the majority of whom were women, 17 lipomas were found; all were submucosal. One-third of the lesions were symptomatic. The most frequent symptoms were abdominal pain, rectal bleeding and a change in bowel habit. Only one patient had multiple lesions. The right colon was most frequently affected.

Five patients underwent major colonic resection either because the diagnosis was confused with carcinoma or because of intussusception. Only one patient was treated by colotomy and polypectomy.

Although most lipomas are small and asymptomatic, tumours larger than 2 cm tend to produce complications or be confused with carcinoma.

Les auteurs font état de leur pratique dans le traitement des lipomes du côlon à l'Hôpital général de St-Boniface, à Winnipeg, Manitoba, entre 1974 et 1985. Ils comparent leur évaluation clinico-pathologique avec celle qui est décrite dans la presse médicale.

Dix-sept lipomes, tous sousmuqueux, ont été retrouvés chez 15 patients (âge moyen 66.7 ans), de sexe feminin surtout. Le tiers des lésions était symptomatique. Douleur abdominale, saignement rectal et modification du transit intestinal représentaient les symptômes les plus fréquents. Un seul patient avait des lésions multiples. Le côlon droit était le plus fréquemment affecté.

Cinq patients ont subi une résection colique importante, soit parce que le diagnostic laissait croire à un carcinome, soit à cause d'une intussusception. Un seul patient fut traité par colotomie et polypectomie.

Même si la plupart des lipomes sont petits et asymptomatiques, les tumeurs de plus de 2 cm tendent à causer des complications ou à être confondues avec un carcinome.

Lipomas of the colon are uncommon. Their clinical importance arises from the difficulty in differentiating them from carcinoma and a tendency for them to produce complications when they are large enough to be symptomatic. As a result, patients have undergone major surgical procedures for a benign condition. This paper reviews our experience at St. Boniface General Hospital in Winnipeg with lipomas of the colon encountered during the period 1974 to 1985 and compares our clinicopathologic evaluation with that found in the literature.

Patients

The study involved all patients with a pathological diagnosis of lipoma of the colon whether symptomatic or found incidentally in surgical specimens or at autopsy.

Findings

We found 17 lipomas in 15 patients (9 women and 6 men) aged from 43 to 81 years (mean 66.7 years). Ten patients were over 60 years of age. Five patients were symptomatic; the most frequent symptoms were abdominal pain, rectal bleeding and change in bowel habit. Of those with symptoms, 40% presented with intussusception. In one case a lipoma obstructed the appendiceal lumen causing appendicitis.

The diameter of 14 lipomas measured ranged from 0.8 cm to 5.5 cm (mean 2.2 cm). Four of the five causing symptoms were larger than 2 cm; the fifth, whose size was not reported, was the lesion causing appendiceal obstruction. In the two cases of intussusception, the lipomas were larger than 4 cm.

All tumours reported in this series were submucosal and composed of adult-type fatty tissue with no sarcomatous change. Multiple lesions (three in the cecum) were found in only one patient. Lipomas occurred more frequently in the right colon, with the cecum and ascending colon each accounting for 29.4% of the total. There were associated colonic carcinomas in six patients, pancreatic carcinoma in one and ovarian cancer in another.

Five of the lesions were seen on barium enema study as filling defects. All were larger than 2 cm and none was diagnosed as a lipoma. The two causing intussusception were diagnosed correctly on barium enema examination.

Two patients underwent colonoscopy; the lesion was noted but not recognized as a lipoma. Biopsy specimens appeared normal. In one patient with a rectosigmoid carcinoma an associated lipoma (2×1.5 cm) was not mentioned on the sigmoidoscopy report.

In this series, only one patient underwent colotomy and excision of a lesion in the ascending colon, diagnosed as a lipoma by palpation at laparotomy. Three patients had either sigmoid resection or right hemicolectomy because the barium enema study showed a filling defect presumed to be carcinoma. The two with intussusception required bowel resection.

Discussion

Lipomas of the colon, although infrequent, are second only to adenoma-

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tous polyps as the most frequent benign bowel tumours.[1,2] The true incidence has not been established but is reported in autopsy series to vary between 0.035% and 4.4% (Table I).[1,3,4] Most reported cases are associated with complications requiring surgery.[4] The etiology and pathogenesis are not known.[5] Approximately 65% of lipomas of the gastrointestinal tract are in the colon.[5-7]

As in this series, many authors[1,2,5,6,8] have reported a 1.5 to 2-fold increase in occurrence in women, but this preponderance is less marked on review of all available series. Women are affected in 53.6% and men in 46.4% of cases (Table I). Most lipomas occur in the fifth to seventh decades, the average age being 63.3 years (Table I), a time when differentiation from carcinoma is critical.

Colonic lipomas occur most often in the right colon (40% to 68%)[1,5,7,9,10] (Table II). This distribution is the reverse of both carcinoma and adenomatous polyps.[11-13] It has been stated that 90% of these lesions are submucosal and 10% subserosal.[4,7,14] Available data indicate, however, that submucosal lesions are found in 95.6% of cases (Table III). The average size is 3.25 cm (Table III). Multiple lesions, which are found mostly in the right colon and are submucosal, occur in 15% of cases (Table III).

Table I—Incidence of Colonic Lipomas and Distribution by Age and Sex

Series	No. cases	Incidence, %	Age, yr		Sex, %	
			Range	Mean	F	M
Long and colleagues, 1949[14]	33	0.5 autopsy	—	54	54.5	45.4
Weinberg and Feldman, 1955[4]	58 autopsy 78 collected series	4.4 autopsy 0.2 collected series	—	—	—	—
D'Javid, 1960[8]	278	—	10 mo – 87 yr	55	62.6	37.4
Haller and Roberts, 1964[1]	20	0.32 autopsy 2.1 surgical	—	70.7	75	25
Wychulis and colleagues, 1964[2]	67	—	40 – 85	62.5	43.3	56.7
Castro and Stearns, 1972[5]	45	—	41 – 84	62.6	60	40
De Beer and Shinya, 1975[25]	22	0.83 colonoscopic exam	49 – 80	66	54.5	45.4
Jaworski, 1980[10]	6	—	—	72	0	100
Michowitz and colleagues, 1985[18]	22	—	41 – 74	60	72.7	27.3
Present study	15	—	43 – 81	66.7	60	40
Average		1.74 autopsy		63.3	53.6	46.4

Table II—Location of Colonic Lipomas

Series	No.	Appendix	Ileocecal valve	Cecum	Ascending colon	Transverse colon	Descending colon	Sigmoid	Rectum
Weinberg and Feldman, 1955[4]	58 (autopsy) lipomas, 4 not localized	—	—	39	6	5	2	1	1
	78 lipomas collected series, 9 not localized	—	—	18	10	19	16	4	2
D'Javid, 1960[8]	278 cases, 4 not localized	1	16	68	37	56	39	41	16
Haller and Roberts, 1964[1]	29 lipomas	0	0	12	9	7	0	1	0
Wychulis and colleagues, 1964[2]	76 lipomas	0	Excluded	21	11	17	12	12	3
Castro and Stearns, 1972[5]	45 cases, plus 4 multiple locations	0	3	9 plus 3 cecum and ascending colon	6	6	2	7	5
De Beer and Shinya, 1975[25]	23 lipomas	0	0	13	5	3	1	1	0
Michowitz and colleagues, 1985[18]	22 cases	0	0	10	5	4	2	1	rectosigmoid
Present study	17 lipomas	1	2	5	5	2	0	2	0

Table III—Gross Pathologic Features of Colonic Lipomas

Series		Size, cm		Multiple, %	Submucosal, %	Subserosal, %
		Range	Average			
Long and colleagues, 1949[14]		—	—	—	94	6
Weinberg and Feldman, 1955[4]		—	4.0	—	—	—
Haller and Roberts, 1964[1]		0.6 – 5.0	—	35	—	—
Wychulis and colleagues, 1964[2]		0.3 – 10	2.72	13.4	—	—
Castro and Stearns, 1972[5]		0.5 – 8.0	3.0	24.4	97.8	2.2
De Beer and Shinya, 1975[25]		1 – 3	2.3	4.5	—	—
Jaworski, 1980[10]		2.2 – 6.0	3.5	0	100	0
Michowitz and colleagues, 1985[18]	Sympt.	0.4 – 2.1	1.25	18	86.3	13.6
	Asympt.	1.7 – 12.4	7.05			
Present study		0.8 – 5.5	2.2	6.7	100	0
Average			3.25	14.6	95.6	4.4

Typically, lipomas are localized encapsulated lesions, either sessile or pedunculated, composed of adult-type fat cells[4,14] (Figs. 1 to 3). Although they frequently undergo ulceration, necrosis, inflammation or cystic degeneration, there is little tendency to become malignant. Castro and Stearns[5] knew of one unreported case of liposarcoma complicating a lipoma. Snover[15] reported two cases of pseudosarcomatous atypia secondary to ulceration and stressed the importance of recognizing such changes as reactive.

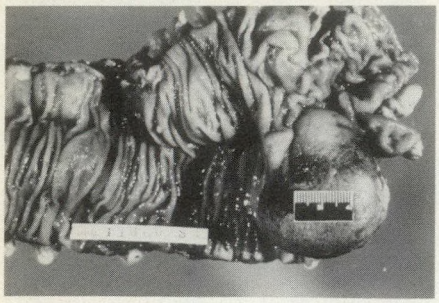

FIG. 1 — Submucosal lipoma of ileocecal valve, measuring 5.5 × 5.0 × 3.5 cm caused cecocolic intussusception with rectal bleeding and large-bowel obstruction.

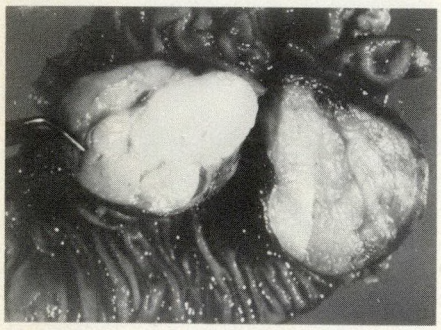

FIG. 2 — Cross-section of lesion in Fig. 1.

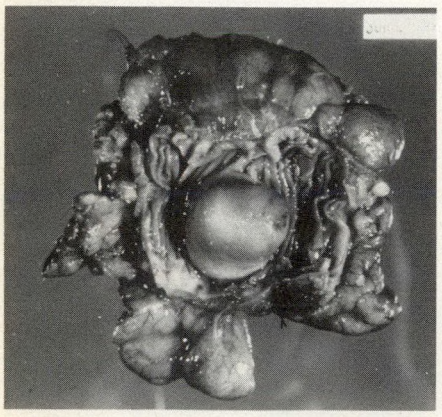

FIG. 3 — Submucosal lipoma of sigmoid colon (3 cm in diameter) caused altered bowel habits.

Reported series indicate that 47% of patients with lipomas are symptomatic and 53% asymptomatic (Table IV). Symptoms are directly related to size[7,12] and caused by tumours measuring 2 cm or more in diameter.[3,5,6,12,16] The most frequent symptoms are abdominal pain 68%, change in bowel habit 64% and rectal bleeding 44% (Table IV); they can be attributed to protrusion of the mass into the bowel lumen, due to colonic motor activity and contraction of the muscularis mucosae, causing luminal obstruction or forming the leading point for an intussusception. Secondary traumatic inflammatory changes result in necrosis, ulceration and hemorrhage. Robertson and colleagues[17] reported a case of spontaneous expulsion of a tumour presumably following this sequence of events.

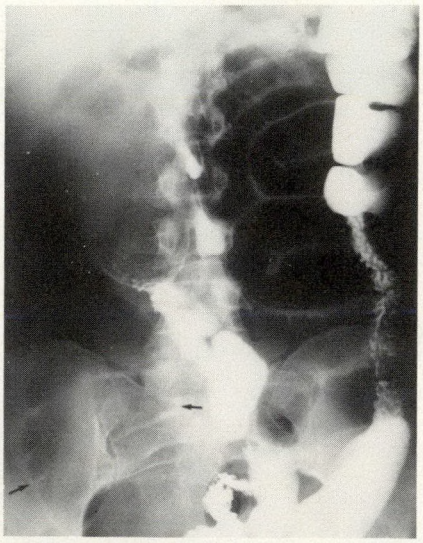

FIG. 4 — Submucosal lipoma of colon causing intussusception with large- and small-bowel obstruction (arrows).

Rectal bleeding secondary to lipoma is usually slow, leading to chronic iron deficiency anemia, and may occur even when the mucosa appears intact.[6] D'Javid[8] reported that the incidence of bleeding increased distally in the bowel as stools became hard, dry and abrasive. Several cases of life-threatening hemorrhage have been reported.[5,8,19]

Lipomas are the most frequent cause of intussusception in adults.[7,12,20] Mayo and colleagues[16] estimated that 50% of clinical lipomas present as an intussusception. However, we found lower values of 0% to 40% with an average of 17.7% (Table IV). Most palpable masses are produced by an intussusception.[4,8] Figure 4 shows the appearance at barium enema examination of a lipoma of the colon causing intussusception and subsequent bowel obstruction.

Less frequent complications of lipomas include protrusion from the anus,[21] rectal prolapse and appendiceal obstruction.[4]

Barium enema is the most frequent examination performed (Table V). Here the lesion may be seen as a smooth, sharply demarcated intraluminal filling defect. The adjacent bowel wall is normally distensible and contractile with intact mucosa.[22] The most characteristic diagnostic finding is that, unlike other tumours, the shape of the filling defect is not constant.[11,23] It is round or ovoid during the filling phase but assumes a distinctly elongated configuration during evacuation (squeeze sign).[13,22] Barium enema studies may not always be diagnostic of lipoma but are necessary to rule out carcinoma. LoIudice and Lang[24] reported a case of a colonic

Table IV—Symptoms and Signs of Colonic Lipomas and Correlation With Size

Series	Symptomatic, %	Asymptomatic, %		Symptoms, %				Size of symptomatic lesions, no./total no.		
		Autopsy	Incidental	Abdominal pain	Rectal bleeding	Intussusception	Change in bowel habit	> 2 cm	< 2 cm	Not specified
Long and colleagues, 1949[14]	75.8		24.2	80.6	35.5	32.2	83.9			
D'Javid, 1960[8]	—	—	—	75.5	49.6	33.0	50.3			
Haller and Roberts, 1964[1]	15	55	30	100	33.3	0	100	3/3	0/3	0/3
Wychulis and colleagues, 1964[2]	56.7		43.3	55.3	44.7	7.9	63.1			
Castro and Stearns, 1972[5]	26.6	20	53.3	66.7	33.3	25.0	33.3	9/12	2/12	1/12
De Beer and Shinya, 1975[25]	32	68		71.4	42.8	0	57.1			
Jaworski, 1980[10]	100	0		50.0	50.0	16.7	83.3	6/6		
Michowitz and colleagues, 1985[18]	36.4	63.6		50	62.5	4.5	62.5			
Present study	33.3	6.7	60.0	60	40	40	40	4/5	0/5	1/5
Average	47	53.0		67.7	43.5	17.7	63.7			

Table V—Radiologic Diagnosis by Barium Enema

Series	No. of lesions seen	Diagnosis of lipoma	Size if seen, cm
Long and colleagues, 1949[14]	28	1 positive 2 likely	—
Haller and Roberts, 1964[1]	18	4 suspicious of lipoma	All > 2
Wychulis and colleagues, 1964[2]	34	4	—
Castro and Stearns, 1972[5]	15	None	—
De Beer and Shinya, 1975[25]	7	—	—
Jaworski, 1980[10]	4	None	—
Michowitz and colleagues, 1985[18]	8	5/8 positive	—
Present study	5	None	All > 2

lipoma producing an apple-core defect on barium x-ray study and simulating carcinoma. Lesions less than 2 cm in diameter are not usually visible.[1] Since the fatty lucency of a lipoma cannot be appreciated on barium studies, a water enema using low kilovoltage x-rays was advocated but has fallen out of favour due to the difficulty of the technique.

Endoscopy has proven to be of some value in the diagnosis when the typical appearance is that of a smooth wide-based polyp, orange red at the tip due to blood vessels coursing over the surface, progressing to a yellow colour at the base. Several techniques may aid in the diagnosis: the pillow or cushion sign,[25] the tenting sign[25] and the naked fat sign pathognomonic of lipoma.[20]

Computed tomography is considered highly successful in the diagnosis of lipomas. Megibow and colleagues[26] and Heiken and colleagues[27] reported six cases in which a diagnosis of lipoma by enhanced computed tomography was made by demonstrating a filling defect with negative attenuation numbers indicating fat. Four of these cases were confirmed at endoscopy or surgery. In addition, Ho and associates[28] reported on a patient who had simultaneous lipoma and adenomatous polyps; computed tomography permitted their differentiation by appearance and attenuation number.

The management of colonic lipomas is primarily surgical but those discovered at endoscopy may be removed by electrocautery snare.[12,22] Although some[12,23] advocate conservative treatment, most[2,5,6,19,29] agree that surgical intervention is indicated in suspected or proven lipoma, not only to provide absolute differentiation from carcinoma but to prevent complications that may necessitate more extensive surgical procedures later. Definitively diagnosed lipomas should be treated by colotomy and excision; large tumours, multiple tumours or intussusception need segmental resection and end-to-end anastomosis.

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Early Results With the J-Pouch Procedure in Children

Mucosal proctectomy with J-pouch construction and ileostomy were performed on eight patients (age range from 4 to 18 years), five with ulcerative colitis and three with familial polyposis coli.

Complications of the first stage included transient neuropraxia of the lateral popliteal nerves, partial dehiscence of the ileoanal anastomosis and prolapse of the loop ileostomy.

The ileostomy was closed 2 to 7 months after initial surgery and was associated with four further complications: enterocutaneous fistula at the ileostomy site, early and late bowel obstruction and pouchitis. Stool frequency decreased as the length of follow-up increased: 3 to 4 stools daily for three children at 2 years postoperatively compared with 4 to 10 stools daily in all children 1 month after surgery.

Functional results were satisfactory and all patients preferred the J pouch to an ileostomy.

Une proctectomie muqueuse avec construction d'un sac en J et iléostomie ont été pratiquées chez huit patients (âgés de 4 à 18 ans), dont cinq malades souffrant de colite ulcéreuse et trois de polypose colique.

Les complications de la première étape opératoire comprennent une neuropraxie transitoire des nerfs poplités latéraux, une déhiscence partiel de l'anastomose iléo-anale et un prolapsus de l'anse de l'iléostomie.

L'iléostomie fut refermée de 2 à 7 mois après la chirurgie initiale et cette intervention fut rattachée à quatre nouvelles complications: une fistule entéro-cutanée au point d'iléostomie, des obstructions intestinales immédiate et retardée et une infection de la poche d'iléostomie. La fréquence des selles a diminué avec la durée de la période de surveillance: 3 à 4 selles quotidiennes chez trois enfants 2 ans après l'opération, comparativement à 4 à 10 selles quotidiennes chez tous les enfants après 1 mois.

Les résultats fonctionnels ont été satisfaisants. Tous les patients ont préféré le sac en J à l'iléostomie.

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Recently there has been renewed interest in restorative proctocolectomy with ileoanal anastomosis to treat ulcerative colitis and familial polyposis coli. In theory, this procedure can eliminate all the diseased colonic mucosa, preserve normal anorectal function and avoid the need for a permanent ileostomy. The operation may be performed with a straight ileoanal anastomosis without an internal reservoir pouch[1,2] or with a reservoir constructed from terminal ileum. The pouch may be in the shape of a J as described by Utsunomiya and colleagues,[3] an S as described by Parks and associates[4] or two, separate, parallel limbs of ileum as described by Ferrari and Fonkalsrud.[5] This report describes the use of the J pouch in children. I chose the J pouch because it was simple to construct, seemed to result in less diarrhea than the straight ileoanal anastomosis and allowed spontaneous evacuation of stool, which is not always possible with the S pouch.[4]

Patients and Methods

Eight consecutive children (five boys and three girls) were operated on over a 2-year period, beginning in June 1983. Five had ulcerative colitis and three had familial polyposis coli. The J pouch was constructed at a mean age of 11 years (range from 4 to 18 years) and in all cases was done in two stages. The first stage consisted of mucosal proctectomy, construction of the J pouch, endorectal pull-through, ileoanal anastomosis and proximal diverting ileostomy. The ileostomy was closed at a second procedure a few months later. All patients with ulcerative colitis had undergone a previous subtotal colectomy and Brooke ileostomy. Patients with familial polyposis coli underwent abdominal colectomy at the time of the restorative proctocolectomy and had not had a previous ileostomy.

Operative Procedure

For the first stage, broad-spectrum antibiotics (usually ampicillin, clindamycin and gentamicin) were prescribed, beginning 1 hour before surgery and continuing for 5 to 7 days. No attempt was made to reduce the rectal inflammation in patients with ulcerative colitis.

In the first two cases, the children were placed in Lloyd-Davies stirrups on the operating table from the onset whereas the last six were left supine until the mucosal dissection and construction of the J pouch were completed. They were then placed in the lithotomy position, in Lloyd-Davies stirrups, for the pull-through and ileoanal anastomosis.

The abdomen was opened through a long midline incision and the rectosigmoid mobilized down to the level of the peritoneal reflection. From the abdominal approach, the outer layers of the rectum were then divided circumferentially down to the mucosa with a scalpel, and the mucosa was stripped from the muscle cuff to the dentate line. No other dissection was necessary within the pelvis. The rectal muscle cuff was left intact from the peritoneal reflection to the level of the internal anal sphincter.

The ileostomy was taken down and a point 10 to 20 cm from the terminal

ileum chosen for the apex of the pouch. The small-bowel mesentery was mobilized to allow this point to come at least 2 or 3 cm below the symphysis pubis. The J pouch was constructed according to the method of Utsunomiya and colleagues,[3] the two limbs being 10 to 20 cm in length, depending on the size of the patient. A quarter-inch Penrose drain was placed through the mesentery and around the apex of the J and pulled through the anus to position the pouch for ileoanal anastomosis. In the first two patients a GIA stapler was used to construct the pouch; in the last six it was constructed by hand, using two layers (outer interrupted, inner continuous) of 3-0 Vicryl sutures. The latter method is almost as fast as the stapler, eliminates the potential for leaks between the staple lines and allows more accurate apposition of the antimesenteric borders of the two limbs of the J.

The patient was then placed in the Lloyd-Davies stirrups and the rectal mucosa everted and excised at the dentate line from below, as in a Soave procedure for Hirschsprung's disease.[6] Special care was taken to remove all of the rectal mucosa. The J pouch was then pulled through the rectal muscle cuff making sure that there was no rotation. The apex of the pouch was opened and the ileoanal anastomosis made at the dentate line with a single layer of interrupted 3-0 Vicryl sutures, taking fairly large tissue bites on both sides. Three stitches were placed in each quadrant of the anastomosis.

The muscle cuff was divided by electrocautery in the posterior midline to the level of the coccyx and allowed to slip down to the floor of the pelvis to prevent the cuff from limiting J-pouch distension. No attempt was made to stitch the muscle cuff around the pouch. Two flat Jackson–Pratt drains were placed deep in the pelvis beside the pouch and brought out through a separate stab incision in the left lower quadrant; none were brought through the perineum. All drains were removed in 2 to 4 days or when they had stopped draining.

A proximal loop ileostomy was brought out in the right lower quadrant and anchored to the skin with interrupted 3-0 Vicryl sutures. A strut left through the mesentery to prevent retraction of the stoma was removed 5 to 7 days later.

The first rectal examination was performed 3 to 4 weeks after operation at which time the ileoanal anastomosis was inspected and palpated. If healing was satisfactory, a contrast roentgenogram of the pouch was obtained to detect any leaks.

No attempt was made to dilate the pouch with either a balloon or instillations through the ileostomy. No sphincter exercises were used.

The patients were readmitted for closure of the ileostomy an average of 4 months (range 2 to 7 months) after proctocolectomy, when both clinical examination of the anastomosis and radiologic examination of the pouch indicated complete healing. At operation, the pouch was inspected endoscopically using a flexible sigmoidoscope. If the pouch was intact and the mucosa was healthy, the ileostomy was closed in a standard fashion.

No special diets or dietary restrictions were applied. No antidiarrheal medications were given for the first 10 to 14 days. Thereafter, loperamide and bulk-forming agents were used as required. The patients were reassessed clinically 1, 3, 6 and 12 months after ileostomy closure. Their functional status was determined by number of stools, fecal incontinence, need to use perineal pads or diapers, ability to distinguish feces from gas and need for medications. After the first year, the patients were reassessed every 12 months by flexible sigmoidoscopy and by evaluation of function.

Results

All patients underwent closure of their ileostomies, were satisfied with the results of the procedure and were functioning normally (Table I). One works full-time as a bricklayer's helper and seven are in school.

Complications

There were no intrapelvic leaks, abscesses or other septic complications; however, major problems were common. The first two patients, who were in the lithotomy position throughout the operation, suffered transient neuropraxias involving the lateral popliteal nerves of both legs. They have since fully recovered. Although the legs were well padded, this complication was probably due to the unusually long time (about 6 hours) spent in the stirrups. None of the remaining six had any neurologic problems.

One child had partial dehiscence of the ileoanal anastomosis which was visible on perineal inspection. This healed slowly by secondary intention, and the ileostomy was successfully closed 4 months later.

The ileostomy was too proximal in one child, who needed several admissions because of dehydration due to high ileostomy losses. The problem resolved after closure of the ileostomy. In one patient the loop ileostomy prolapsed, necessitating reoperation. In another, an enterocutaneous fistula developed at the site of the ileostomy closure, but it healed spontaneously.

After closure of the ileostomy one child suffered a partial obstruction in the afferent loop to the pouch necessitating reoperation. The bowel was divided longitudinally where the afferent loop entered the pouch and was closed transversely in the manner of a Heineke–Mikulicz pyloroplasty. This closure was protected by reconstructing the loop ileostomy. Nine months later, the ileostomy was reclosed and the child now has good function.

There were two major late complications. One child had an adhesive small-bowel obstruction, which necessitated enterolysis, the other had mild weight loss and minor rectal bleeding due to pouchitis. In the latter there was marked friability and redness of the pouch mucosa on endoscopy. Biopsy of the mucosa showed a nonspecific inflammation, but cultures of the stool grew normal fecal flora. The patient responded well to a course of metronidazole taken orally.

Function

In general, the functional results

Table I—Patient Summary

Patient no.	Age, yr	Sex	Indications for colectomy	Colectomy to J pouch interval, mo	J pouch to ileostomy closure interval, mo
1	15	M	Chronic ulcerative colitis	10	2
2	18	M	Familial polyposis coli	—	7
3	12	F	Familial polyposis coli	—	2
4	4	M	Chronic ulcerative colitis	18	6
5	10	F	Chronic ulcerative colitis	18	4
6	12	M	Chronic ulcerative colitis	9	3
7	11	M	Familial polyposis coli	—	2
8	7	F	Chronic ulcerative colitis	8	4
Mean ± SEM	11 ± 2			13 ± 2	4 ± 1

were excellent. After the first-stage operation most patients experienced discharge of mucus through the anus, which was difficult to control. One passed stool per rectum before closure of the ileostomy, presumably because of spillover past the loop.

All patients were able to defecate spontaneously and distinguish feces from gas. None required rectal intubations or irrigations. Stool frequency and continence are summarized in Tables II and III. The two patients who required diapers at night were the youngest in the series. One had ulcerative colitis at 1 year of age and underwent colectomy a year later, before being toilet trained. He is now continent during the day but still wears a diaper at night. The second, who also had ulcerative colitis, was aged 7 years at the time of her pull-through. She is continent during the day but wears a diaper at night because of occasional gross fecal incontinence.

Discussion

Although these initial results are satisfactory, there are several obvious drawbacks to widespread adoption of the J-pouch procedure. The morbidity is high, the functional results are less than perfect and the long-term results unknown.

One technical point is of interest. Others[7] have preferred to remove the entire rectal wall down to the level of the levator ani muscles and to remove the distal rectal mucosa using the perineal approach. This is quicker and may allow the pouch to distend more easily in the pelvis. However, the extracolonic dissection carries with it the risk of injuring the pelvic autonomic nerves, as described by Neal and colleagues.[8] Most pediatric surgeons experienced in performing the Soave procedure for Hirschsprung's disease will likely find it easier to do the endorectal dissection from above.

The morbidity was high in this series, but most of the complications were either self-limiting or easily corrected. Pouchitis may be the most serious complication of all. Its true incidence, cause and natural history are unknown; it can be insidious. The one patient who had this complication was only mildly symptomatic with slight weight loss and rectal bleeding. He did not have diarrhea, but the degree of inflammation of the pouch mucosa was extreme. Pouchitis may go undetected unless routine endoscopic examination is performed.

Most reports on restorative proctocolectomy have indicated that stool frequency decreases markedly with time. This was not obvious in our series. In fact, the initial daily stool frequency 1 month after closure of the ileostomy averaged only 6 (range from 4 to 10). However, with time there was a gradual improvement in the rectal urgency and less need for antidiarrheal medication. These patients pass stools about as frequently as patients with ileostomy empty their appliance. In a follow-up study of 675 patients who had undergone proctocolectomy and Brooke ileostomy at the Mayo Clinic, Pemberton and colleagues[9] found that most patients emptied their appliances four to eight times daily (median six times).

The children and their parents preferred the functional results of the J-pouch procedure to the previous ileostomy although the results appear to be a little disappointing since most patients had some night-time soiling and two wore pads or diapers at night after 6 months. However, the soiling was minor except in the two youngest patients, already mentioned, who required toilet training after ileostomy closure.

The initial choice of the J pouch was supported by the fact that stool frequency did seem to be lower than reported for the straight ileoanal anastomosis without an internal pouch.[2] This was also noted by the Mayo Clinic group.[10] They concluded that this was because there is decreased peristalsis and greater degree of compliance to distension with the pouch than with the straight ileoanal anastomosis.[11]

All patients in the present series were able to empty their pouch spontaneously and none required intubation for evacuation, as has been reported with the S pouch.[4]

This paper was prepared with the assistance of the Medical Publications Department, The Hospital for Sick Children, Toronto, Ont.

Table II—Mean Stool Frequency During Follow-up Period

Months after ileostomy closure (no. of patients)	Mean no. of stools per patient			
	Day	Night	Total	Range
1 (8)	5	1	6	4 – 10
6 (7)	5	1	6	4 – 9
12 (5)	5	0	5	3 – 10
24 (3)	3	0	3	3 – 4

Table III—Functional Status During Follow-up Period

Months after ileostomy closure (no. of patients)	No. of patients with functional status				
	Soiling		Pad/diaper		On medication
	Day	Night	Day	Night	
1 (8)	2	6	0	2	6
6 (7)	2	4	0	2	3
12 (5)	1	2	0	1	2
24 (3)	0	0	0	0	0

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Announcing a transformation of parenteral antibiotic therapy

PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

the first carbapenem antibiotic

* ® Trademark

PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

A carbapenem, representing a totally new class of antibiotics

The broadest spectrum single-agent antibiotic

possessing bactericidal activity against a great majority of clinically significant pathogens

PRIMAXIN* offers the activity of

the penicillins against gram-positive aerobes – including coverage of *Streptococcus faecalis*

plus

the aminoglycosides and 3rd generation cephalosporins against gram-negative aerobes – including coverage of *Pseudomonas aeruginosa*

plus

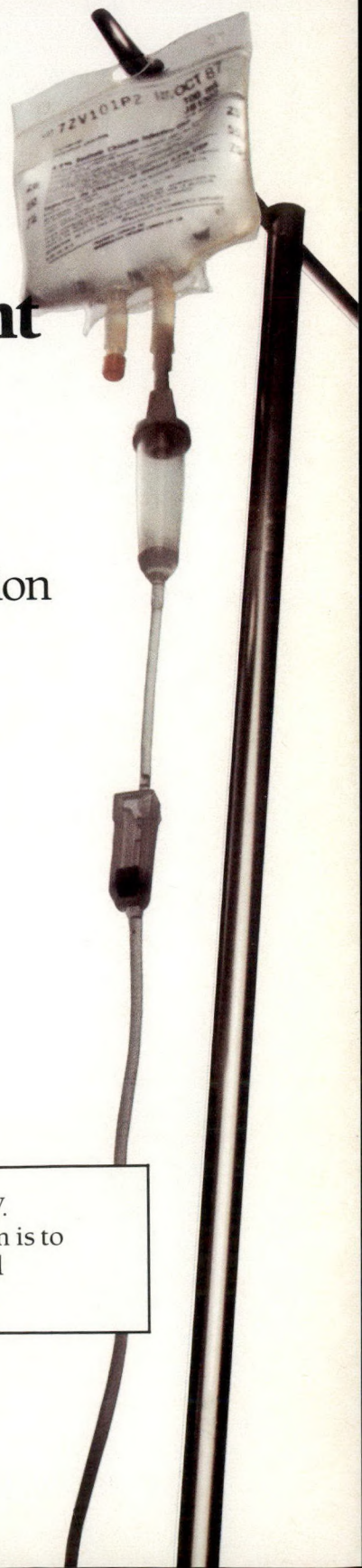
the antianaerobic agents – including coverage of *Bacteroides fragilis*

PRIMAXIN* is not active against *Corynebacterium* group JK, *Fusobacterium varium*, *Mycobacterium* spp., *Chlamydia* spp., *Streptococcus faecium*, *Pseudomonas maltophilia*, and some strains of: *P. cepacia*, *P. pseudomallei*, methicillin-resistant staphylococci, and *Flavobacterium* spp.

Single-agent antibiotic for documented and empiric therapy in many important infections†

including

- infections usually treated with combination therapy
- infections complicated by underlying disease
- nosocomial infections

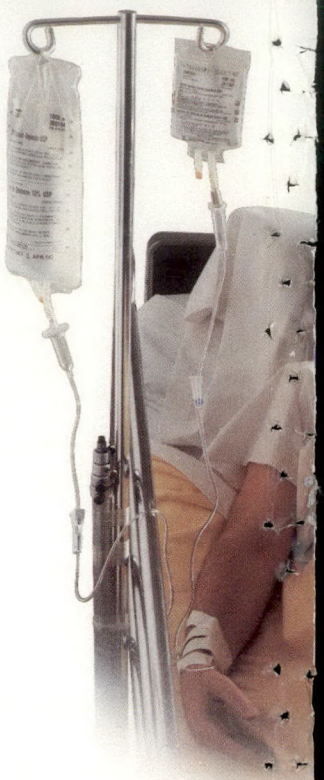


Imipenem and cilastatin sodium are present in a 1:1 ratio in PRIMAXIN* I.V. Imipenem is the sole antibacterial component. The role of cilastatin sodium is to prevent the inactivation of imipenem in the kidney and obtain antibacterial concentrations of imipenem in the urine.

†Caused by organisms susceptible to PRIMAXIN* I.V.

PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)



Clinical efficacy in many important infections†

EFFICACY IN INTRA-ABDOMINAL INFECTIONS[1]

91% cure or improvement

in 164 evaluable patients

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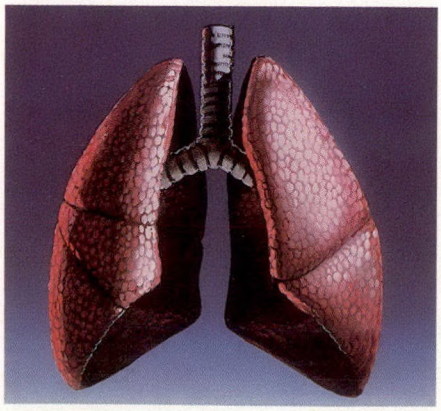
EFFICACY IN LOWER RESPIRATORY TRACT INFECTIONS[2]



85% cure or improvement

in 204 evaluable patients

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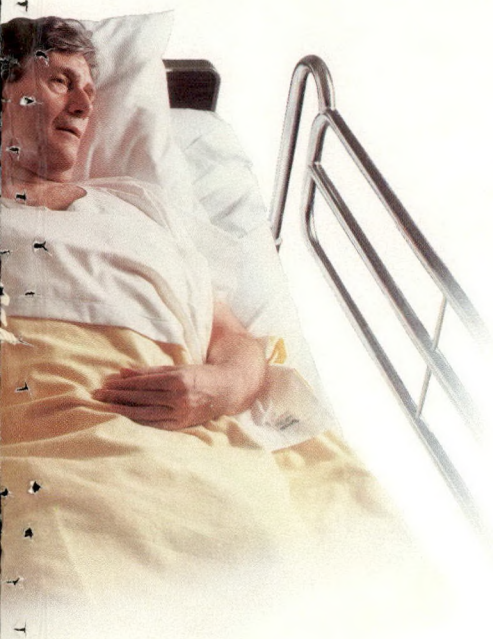
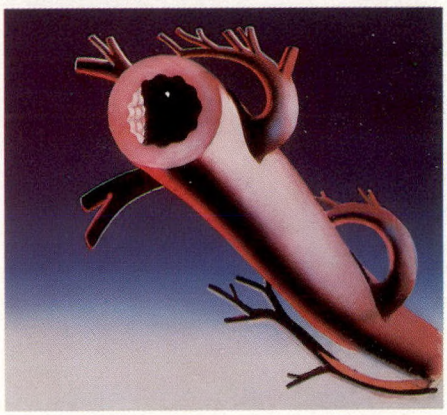
†Caused by organisms susceptible to PRIMAXIN* I.V.



EFFICACY IN BACTERIAL SEPTICEMIA[3]

90% cure or improvement
in 135 evaluable patients



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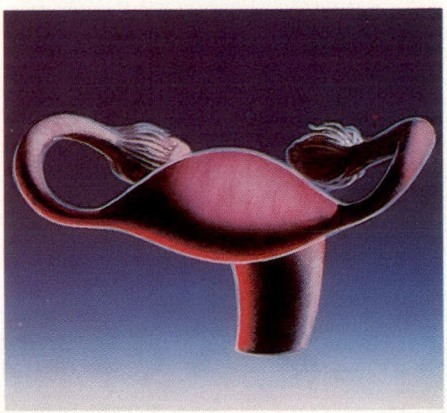
EFFICACY IN GYNECOLOGICAL INFECTIONS[4]

97% cure or improvement
in 72 evaluable patients



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PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

PRIMAXIN* I.V. offers management advantages over combination therapy that includes an aminoglycoside

Generally well tolerated – safety profile similar to cefazolin[5]

- 1723 patients, including the severely ill, have received therapy in clinical trials. The incidence of the most common adverse experience (nausea) was no greater than 2%.
- Avoids the potential nephrotoxicity or ototoxicity experienced with aminoglycosides.
- Avoids the potential hypoprothrombinemia and clinical bleeding experienced with cephalosporins with MTT† side chain.
- Avoids the potential disulfiram-like effect experienced with metronidazole and cephalosporins with MTT side chain.

Convenience of a single agent

The broadest spectrum single-agent antibiotic representing a transformation of parenteral antibiotic therapy

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† Certain antibiotics which possess, as part of their molecular structure, the 1-methyl-5-thiotetrazole (MTT) group have been associated with hypoprothrombinemia (and in some cases, clinical bleeding) and with a disulfiram-like effect.

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PRIMAXIN*

(imipenem and cilastatin sodium for injection)

Antibiotic

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

ACTION

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

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

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

INDICATIONS AND CLINICAL USE

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

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

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

Gram-positive Aerobes

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

Gram-negative Aerobes

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

Gram-positive Anaerobes

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

Gram-negative Anaerobes

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

CONTRAINDICATIONS

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

WARNINGS

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

Pseudomembranous colitis

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

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

PRECAUTIONS

General

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

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

Use in Patients with Impaired Renal Function

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

Use in Pregnancy

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

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

Nursing Mothers

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

Pediatric Use

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

Drug Interactions

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

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

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

ADVERSE REACTIONS

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

Local Adverse Reactions

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

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

Systemic Adverse Reactions

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

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

Respiratory

dyspnea	0.1
hyperventilation	<0.1
thoracic spine pain	<0.1

Cardiovascular

hypotension	0.4
palpitations	0.1
tachycardia	<0.1

Renal

oliguria/anuria	<0.1
polyuria	<0.1

Skin

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

Body as a whole

polyarthralgia	<0.1
asthenia/weakness	<0.1

Adverse Laboratory Changes

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

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

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

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

Renal: Increased BUN, creatinine.

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

TREATMENT OF OVERDOSAGE

There are no data available on overdosage.

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

DOSAGE AND ADMINISTRATION

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

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

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

Dosage in Adults

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

Dosage in Elderly Patients

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

TABLE 1

ADULT DOSAGE OF PRIMAXIN*

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

× Primarily some strains of *Ps. aeruginosa*.

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

Dosage in Patients with Renal Insufficiency

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

TABLE 2
MAXIMUM DOSAGE OF PRIMAXIN* IN RELATION TO RENAL FUNCTION

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

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

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

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

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

Females: 0.85 x above value.

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

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

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

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

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

Dosage in Infants and Children

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

Administration

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

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

RECONSTITUTION

Contents of the 13 mL vials must be suspended and transferred to 100 mL of an appropriate infusion solution.

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

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

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

COMPATIBILITY AND STABILITY

List of diluents

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

Reconstituted solutions

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

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

DOSAGE FORMS

AVAILABILITY

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

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

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

STORAGE

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

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Effects of Immobilization and Continuous Passive Motion on Postoperative Muscle Atrophy in Mature Rabbits

The effects of continuous passive motion and cast immobilization on muscle atrophy were compared 3 weeks after bilateral arthrotomies on 10 mature New Zealand rabbits. The gastrocnemius, rectus femoris and tibialis anterior muscles were excised and weighed, and the dry weights of the gastrocnemius were also determined. The protein concentration and cross-sectional areas of types I and II muscle fibres in the rectus femoris and tibialis anterior muscles were measured. Compared with the results in rabbits treated by cast immobilization, continuous passive motion significantly ($p < 0.05$) reduced muscle atrophy as determined from the wet and dry weights of the gastrocnemius muscles, the protein content in the tibialis anterior muscles and the cross-sectional areas of the type II fibres in the rectus femoris muscles.

On a comparé chez 10 lapins de Nouvelle Zélande adultes, les effets de la mobilité articulaire passive continue et ceux de l'immobilisation par plâtrage sur l'atrophie musculaire, 3 semaines après une arthrotomie bilatérale. Les gastrocnémiens, le muscle droit antérieur de la cuisse et le muscle jambier antérieur furent excisés et pesés; on a aussi déterminé le poids sec des gastrocnémiens. La teneur en protéine et les aires transversales occupées par les fibres musculaires de type I et II des muscles droits antérieurs de la cuisse et jambiers antérieurs ont aussi été mesurées. Comparativement à l'immobilisation par un plâtre, la mobilité articulaire passive continue a diminué significativement ($p < 0.05$) l'atrophie musculaire du lapin, tel que le démontrent les poids frais et secs des gastrocnémiens, la teneur en protéine des muscles jambiers antérieurs et les aires transversales des fibres de type II dans les muscles droits antérieurs de la cuisse.

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The time-honoured practice of immobilizing limbs after injuries and operations leads to joint stiffness and atrophy of the muscles,[1-6] with the result that extended periods of rehabilitation are often necessary for the limb to regain normal function. Altered function of a muscle (due to immobilization) affects not only its size and strength, but also its histologic and biochemical characteristics.[3,7-10] Atrophy of a muscle is characterized by an immediate and exponential decrease in its wet weight, total protein content[7] and the cross-sectional area of its fibres.[3,5,11,12] The reduction in wet weight is paralleled by a proportionate reduction in dry weight[6] and protein content.[6,13] The beneficial effects of continuous passive motion (CPM) on articular cartilage and periarticular tissues, and on the regeneration of articular cartilage have recently been demonstrated in animals.[14-26] As a result of these experimental investigations, the concept of CPM has been applied to the care of humans with a variety of disorders and injuries of synovial joints.[25,27,28]

We designed a study to compare the effects of CPM and cast immobilization on muscle atrophy postoperatively.

Materials and Methods

Under general inhalation anesthesia (halothane, nitrous oxide and oxygen), medial arthrotomies were performed on both knee joints of 10 adult male New Zealand rabbits, each weighing between 3.3 and 3.7 kg. After dislocation, then reduction of the patellae, the capsular incisions were closed with continuous 4-0 Vicryl sutures and the skin with continuous subcuticular 4-0 stainless steel sutures.

One of the two limbs was randomly selected to be immobilized in a long-leg plaster cast with the knee held in 80° of flexion and the ankle in 50° of plantar flexion. The rabbit was then placed in the CPM apparatus so that the other limb could be moved passively and continuously for the duration of the experiment, as described previously.[20,29] After 3 weeks of such treatment the animals were sedated, then killed by an intravenous overdose of sodium pentobarbital.

The animals were weighed and the ranges of motion of the ankle and knee joints measured, at least twice, using a goniometer (the median value was used). The tibialis anterior and rectus femoris muscles were dissected free. Anticipating that the cross-sectional areas of the muscle fibres would vary with the degree of shortening or lengthening of each muscle, we controlled this variation by holding the knee and hip joints in 90° of flexion and the ankle joints in 30° of

plantar flexion before we took muscle samples. Furthermore, the length of muscle to be excised was kept constant by fixing the ends of each sample in a specially designed clamp (Fig. 1) before excision. One sample was obtained from the anterior region of the rectus femoris muscle and one from the medial region of the tibialis anterior. While still held in the clamps, each sample was immersed in a bath of isopentane, "snap frozen" in liquid nitrogen, then weighed.

In a cryostate at −25°C, transverse sections, 10 μm thick, were cut from the muscle samples then stained for myofibrillar adenosine triphosphatase activity (preincubation pH 9.4) according to the methods of Padykula and Herman[30] as modified by Guth and Samaha.[31] Using a Bausch and Lomb digital image analyser (System Omnicon 3000; Bausch and Lomb, Rochester, NY) connected to a microscope, we measured the cross-sectional areas of the type I and type II muscle fibres in a randomly selected group of 50 fibres for each type. The remaining parts of the rectus femoris and tibialis anterior and the whole gastrocnemius muscles were carefully excised and blotted dry, and the fat and connective tissue were removed. The wet weight of each specimen was obtained and the samples were then stored on dry ice. For dry weights, the gastrocnemius muscles were diced and dried in an oven at 72°C for 120 hours before weighing.

The protein concentration in a 25- to 30-mg sample taken from the proximal aspects of each of the tibialis anterior and rectus femoris muscles was determined according to the method of Lowry and colleagues,[32] using bovine serum albumin as a standard. Protein levels were measured within 12 hours after the animals had been killed. Since it is necessary to dessicate the whole muscle to obtain its dry weight, this procedure or the combination of protein concentration and muscle fibre size, but not both, could be determined in any one muscle.

The data were analysed using the paired *t*-test, with differences being accepted as significant at a probability level of $p < 0.05$.

Results

Gross Findings

One animal with a dislocated patella was excluded from the analysis. Each animal lost an average of 16% of its original body weight during the experiment.

Range of motion in both the ankle and knee joints was significantly reduced in the limbs treated by cast immobilization, compared with those receiving CPM (Fig. 2).

Wet and Dry Weights

The mean wet weights (± one standard deviation) of the gastrocnemius muscles were 7.58 ± 1.37 g in the cast limbs compared with 9.61 ± 1.97 g in the CPM limbs ($p < 0.05$) (Fig. 3). The wet weights of rectus femoris muscles in the cast limbs (8.02 ± 0.028 g) were lower than those in the CPM limbs (8.30 ± 1.07 g), but this difference was not statistically significant. The wet weights of the tibialis anterior muscles were equal in the cast (4.28 ± 0.76 g) and CPM (4.28 ± 0.96 g) groups. The dry weights of the gastrocnemius muscles were significantly ($p < 0.05$) lower in the cast limbs than in the CPM limbs (1.85 ± 0.34 g versus 2.33 ± 0.50 g) (Fig. 4).

Protein Concentration

The protein concentration, expressed as a percentage of the wet weight of the muscle (grams of protein per gram of muscle), in the tibialis anterior was significantly ($p < 0.05$) lower in the cast group (17.95% ± 1.69%) than in the CPM group (19.64% ± 2.41%). There was no significant difference between the protein concentration in the rectus femoris of the cast (19.47% ± 1.24%) and the CPM (20.21% ± 1.49%) groups.

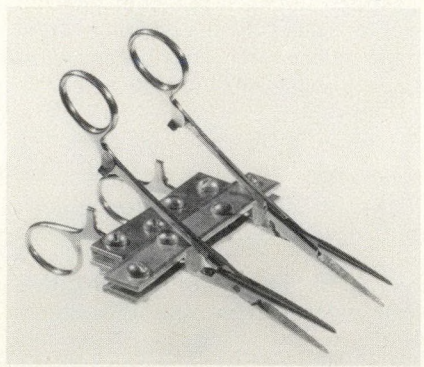

FIG. 1 — Specially designed muscle clamp consisting of two straight hemostats held fixed distance apart by clamp consisting of two metal plates. Ends of muscle sample to be excised were fixed in clamps before excision and held in position during histochemical fixation.

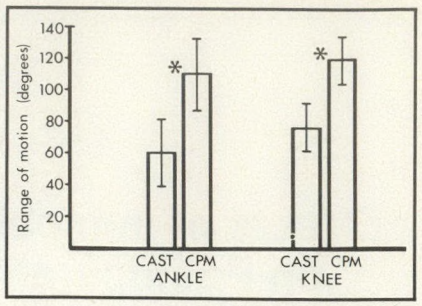

FIG. 2 — Range of motion of ankle and knee joints 3 weeks postoperatively for nine rabbits. Values are mean ± one standard deviation. * = significantly different ($p < 0.05$).

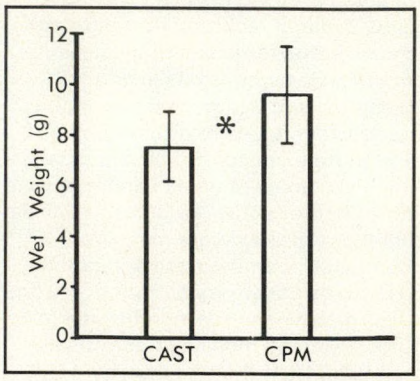

FIG. 3 — Wet weights of gastrocnemius muscles 3 weeks postoperatively (nine rabbits). Values are mean ± one SD. * = significantly different ($p < 0.05$).

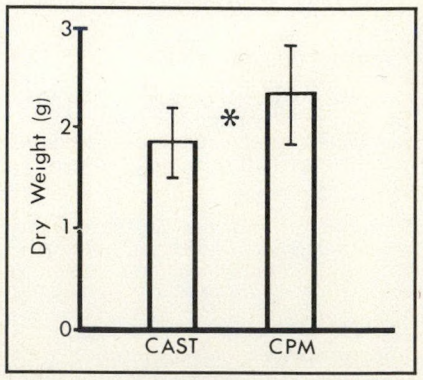

FIG. 4 — Dry weights of gastrocnemius muscles 3 weeks postoperatively (nine rabbits). Values are mean ± one SD. * = significantly different ($p < 0.05$).

Table I—Cross-Sectional Areas of Muscle Fibres in Nine Rabbits*

	Rectus femoris		Tibialis anterior	
Group	Type I	Type II†	Type I	Type II
Cast	3593 ± 1280	2910 ± 555	4237 ± 862	3253 ± 608
CPM	3966 ± 1348	3795 ± 629	3460 ± 450	2750 ± 526

*Values are expressed as the mean ± one SD (in μm^2).
†$p < 0.05$.

Histochemical Findings

The cross-sectional areas of the muscle fibres are listed in Table I. The average cross-sectional areas of both type I and type II fibres in the rectus femoris muscles of the casted limbs were lower than those in the CPM-treated limbs, although the difference was only statistically significant for the type II fibres. Interestingly, this pattern appeared to be reversed in the tibialis anterior muscles although these differences were not statistically significant (Table I).

Discussion

Our experiment demonstrated that gastrocnemius muscles undergo a significantly greater loss of wet and dry weight in limbs that are immobilized postoperatively than do those treated by CPM. Moreover, the cross-sectional areas of the type II fibres in the rectus femoris muscles in the cast group were significantly smaller than those in the CPM group.

Normally, the protein concentration in a muscle is not affected by moderate systemic weight loss.[6,13] However, the protein concentrations in the tibialis anterior muscles were significantly lower in the cast group than in the CPM group, even though the wet weights of these muscles were equal in both groups. Consequently, the total protein content (protein concentration × wet weight of the muscle) was significantly lower in the tibialis anterior muscles from the limbs treated by cast immobilization than in those from the limbs treated by CPM. This could be interpreted to mean that the muscles were edematous, but this would conflict with the observation that the cross-sectional areas of both the type I and type II fibres were slightly, but not significantly, greater in the immobilized tibialis anterior muscles than in the CPM-treated muscles. The latter observation is consistent with the phenomenon of transient hypertrophy, described in muscles that have been immobilized in a position of light stretch.[7,33]

A factor that might have affected the results for the tibialis anterior muscles was that during immobilization these muscles were held under tension. The length of a muscle during immobilization, relative to its resting length, influences the amount of atrophy that will occur. When a muscle is immobilized in a state of relaxation, atrophy will occur in a matter of days.[7,33] However, when a muscle is immobilized in a state of tension, the atrophic changes are preceded by a period of transient hypertrophy.[7,33] This was illustrated in 1957 by Ferguson and colleagues,[4] who demonstrated marked hypertrophy of the tibialis anterior muscle after 3 weeks of cast immobilization with the muscle under tension.

Many authors[5,8,12,13] have related the histochemical changes in cross-sectional areas (or diameters) of the muscle fibres to the other parameters of muscle atrophy, but apparently they gave no consideration to the dependence of these measurements on the length of the muscle at the time of excision and histochemical fixation. We believe that the cross-sectional area or diameter of a muscle fibre should increase if a muscle is allowed to shorten before, or after, excision of the specimen. Therefore, in our study, the joints were held in a similar position in all animals and a specially designed clamp was used to standardize the length of each muscle sample before excision and to maintain this length during histochemical fixation.

A relatively greater degree of atrophy was observed in the type II than the type I fibres of the rectus femoris muscles. Although the explanation for this observation is not clear, others[3,5,12,13] have shown that changes in size with atrophy or hypertrophy depend on many factors and may differ for the two fibre types.

Conclusions

Our investigation has demonstrated that, with respect to wet and dry muscle weight, protein content and histochemical muscle fibre size, atrophic changes in muscles from three major compartments of rabbits' limbs subjected to an operative procedure can be substantially reduced by using continuous passive motion rather than cast immobilization.

Although we cannot extrapolate these findings directly to other clinical situations in which a joint has been injured or inflamed, this conclusion might also be valid for nonoperative abnormalities of synovial joints. For example, CPM has been shown to have a protective effect on articular cartilage in septic arthritis,[22] and to enhance the clearance of synovial effusions and hemarthroses[14,15] and the healing of articular cartilage defects.[19,20,22] These are conditions frequently treated by rheumatologists and orthopedic surgeons, and for which the prescribed treatment traditionally has included resting or splinting the affected joints. The prevention of muscle atrophy is a goal to be considered not only in patients postoperatively, but also in those suffering from acute inflammatory conditions that limit active motion of joints.

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Colonoscopy in the Follow-up of Patients With Colorectal Carcinoma

In an effort to determine the value of colonoscopy in the follow-up of patients who have undergone resection for colorectal carcinoma, the authors evaluated prospectively 100 consecutive patients who, during follow-up after resection for colorectal cancer, had normal findings on barium enema examination and also underwent colonoscopy. The follow-up from operation to colonoscopy ranged from 8 months to 15 years (average 2.6 years). Two recurrent and two metachronous carcinomas were detected. In addition, 25 polyps (3 benign) were removed from 22 patients. Twelve of the malignant polyps were less than 1 cm in dimension, the other 10 were larger. Colonoscopy is considered valuable in this setting for earlier detection and removal of recurrent and metachronous carcinomas and potentially premalignant lesions.

En vue de déterminer l'intérêt de la colonoscopie dans l'examen de contrôle des patients qui ont subi la résection d'un carcinome colorectal, on a évalué de façon prospective 100 patients qui, en cours de surveillance de post-cure, présentaient des résultats normaux au lavement baryté et qui ont aussi subi une colonoscopie. La période écoulée entre l'opération et la colonoscopie a varié entre 8 mois et 15 ans (moyenne 2.6 ans). Deux récidives et deux carcinomes métachrones ont été décelés. De plus, 25 polypes (3 bénins) ont été réséqués chez 22 patients. Douze des polypes malins avaient une taille inférieure à 1 cm; les 10 autres étaient plus gros. Dans un tel contexte, la colonoscopie fut utile puisqu'elle permit la détection de récidives et de carcinomes métachrones, et que plusieurs lésions prémalignes ont été décelées et réséquées.

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It is an established fact that patients who have undergone resection of a colorectal carcinoma run an increased risk of development of a metachronous carcinoma, polyp or anastomotic recurrence.[1-3] The degree of follow-up after resection is controversial. Proponents of intensive follow-up state[4,5] that should a recurrent or metachronous lesion be detected when a patient is asymptomatic, the probability of cure by repeat resection will be increased, since the newly detected lesion will be at a more favourable stage[6] than if the patient were symptomatic. Opponents[7-10] argue that intensive follow-up is not worth the effort and expense, since up to 62%[11] of new lesions will be detected when the patient presents with symptoms between scheduled follow-up sessions.

Among those favouring intensive scrutiny, the method by which it is carried out is under discussion. Some suggest colonoscopy in all cases, with or without barium enema examination because it enables the detection of anastomotic recurrences, metachronous carcinomas or new polyps, which can be removed. Colonoscopy permits the detection of lesions that may have been missed on barium enema study and can more accurately evaluate the nature of suspicious narrowings in the bowel.

The purpose of this prospective study was to determine if colonoscopy was of value in the follow-up of patients who had undergone resection for colorectal carcinoma.

Patients and Methods

The study comprised 100 consecutive asymptomatic patients (57 men, 43 women) who had undergone resection for colorectal carcinoma. They ranged in age from 35 to 82 years (average 63 years). The locations of the primary carcinomas are listed in Table I and the Dukes' staging in Table II.

Scheduled follow-up examinations carried out were as follows: proctosigmoidoscopy, presence of carcinoembryonic antigen, liver function tests and complete blood counts every 3 months for the first 2 years postoperatively, then every 6 months for another 3 years and annually thereafter; chest x-ray every 6 months for 5 years and single-contrast barium enema annually. Subsequently, at varying times postoperatively the patients underwent colonoscopy. Patients with positive findings on barium enema were excluded from the study, since it was our intent to see if by colonoscopy we were able to pick up lesions that were missed on barium enema examination.

A metachronous carcinoma was defined as that occurring more than 1 year after the initial resection.

Results

The colonoscopy was performed from 8 months to 15 years after initial resection (mean 2.6 years). The examination was completed to the cecum in 94% of cases; in the remaining 6% it was considered incomplete because of technical difficulties, patient intolerance or poor bowel preparation.

Colonoscopic findings included two anastomotic recurrences, both of which occurred 1 year after right hemicolectomy. Metachronous carcinomas were detected in two patients, in the ascending colon and cecum, 1 year after sigmoid and low anterior resections respectively. Twenty-five polyps were found in 22 patients; 3 polyps were benign. Twelve of the malignant polyps were found to be less than 1 cm in dimension and 10 were larger than 1 cm. The histologic variety of each polyp is listed in Table III and the location in Fig. 1.

Table I—Location of Primary Carcinomas

Location	No. of patients
Rectum	44
Sigmoid colon	30
Descending colon	6
Transverse colon	5
Ascending colon	10
Cecum	5

Table II—Dukes' Staging of Primary Carcinoma

Stage	No. of patients
A	36
B	37
C	27

Table III—Histologic Type of Polyps Found at Colonoscopy

	Size, cm	
Histologic type	< 1 cm	≥ 1 cm
Tubular adenoma	8	2
Tubulovillous adenoma	4	5*
Villous adenoma	—	3
Hyperplastic	3	—

*1 polyp with carcinoma in situ.

Discussion

After "curative" resection for colorectal carcinoma the goal of follow-up should be the detection of anastomotic recurrences or metachronous lesions at a time when further treatment for cure may be possible.

Whereas it was generally believed that 75% of colorectal carcinomas could be detected with rigid or flexible sigmoidoscopy,[12] a recent shift in the distribution of large-bowel cancer has been observed.[13,14] In our study, nearly 75% of primary carcinomas were in the left colon and malignant lesions that developed after resection were predominantly right sided. Thus, had the traditional methods of follow-up been used, 86% of neoplastic lesions, two metachronous carcinomas and two anastomotic recurrences would have gone undetected until, presumably, symptoms developed.

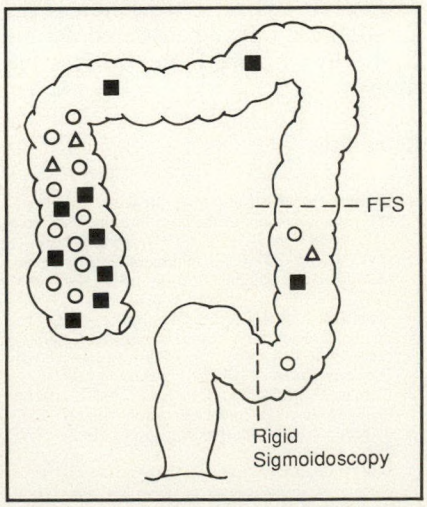

FIG. 1 — Location of polyps found at colonoscopy. Circles = less than 1 cm in dimension, squares = more than 1 cm, triangles = benign polyps. FFS = extent of flexible sigmoidoscopy.

Bühler and colleagues[4] noted that repeat resections for cure were possible in 66% of patients who were asymptomatic at the time the recurrent lesion was detected, but in symptomatic patients the lesion was usually unresectable. Since many reports have documented that most recurrences occur within the first 2 years after resection of the primary lesion,[10,15] it seems reasonable to concentrate follow-up efforts during this period. Those opposed to intensive follow-up[7-11,15] state that the poor reoperation rate for cure, ranging from 7% to 20%, negates the cost and effort applied.

Although follow-up aimed at detecting recurrent disease has met with little success, it has been suggested that intensive scrutiny would be more productively directed toward the detection of metachronous polyps and carcinomas. There is considerable evidence that patients who have had a previous colorectal carcinoma are at risk for metachronous neoplasms since their entire colorectal mucosa seems to be unstable and potentially malignant,[16] the so-called "terrain préparée". It is also accepted that many, if not most, colorectal carcinomas develop from an adenomatous polyp.[17,18]

Although a metachronous lesion is defined as one occurring after resection of the primary carcinoma, some authorities[6] require a 2-year interval before a lesion would be classified as such. Thus, the metachronous neoplasms in our series would be considered as missed synchronous lesions, present at the time of the original resection, and one would be compelled to conclude that barium enema examination failed to detect these lesions, since all patients had the examination before resection. A similar point has been expressed by others.[6,19,20] This would justify colonoscopy preoperatively to clear the colon of all other neoplastic elements. In one report[21] preoperative colonoscopy identified 55% of synchronous neoplasms that were undetected on barium enema examination. Indeed, it may alter the extent of resection in some patients.[21-24]

That the entire colon must be evaluated is not in dispute, rather it is the method by which evaluation is accomplished that is controversial. Two methods are currently available: barium enema and colonoscopy. Both have their limitations.

Although some may take issue with

our use of single-contrast barium enema examination, there is evidence that both single- and double-contrast examinations have almost identical sensitivities for detecting polyps larger than 1 cm in diameter.[25] Double-contrast barium enema is, however, superior in detecting smaller neoplasms (less than 1 cm) and polyps in general, regardless of size.[25] Single-contrast barium enema examination allows diagnosis of most malignant lesions.[25] It is the examination most commonly performed, being less costly, less time-consuming and better tolerated in elderly patients than the double-contrast technique.[25]

The prevalence of carcinoma in small adenomatous polyps is negligible as illustrated by Ott and colleagues[26] in a review of 2344 adenomas; they recorded a rate of invasive malignant disease of 0.09%. The question then arises whether it is necessary to detect polyps less than 1 cm in size. The general consensus appears to be that detection of diminutive adenomas in patients over 70 years old is less crucial because of a limited life span. However, a recent study[27] revealed a 15% incidence of invasive carcinoma in polyps less than 1 cm in size; thus, miniature polyps may be of importance in younger patients. It must be pointed out that this high incidence of carcinoma in small polyps has not been reported by others, and the reason for the discrepancy is unclear.

Colonoscopy, although hailed as the best diagnostic tool available to evaluate the entire colon,[28] is not infallible. It, too, has several "blind spots" where lesions may be overlooked. For polypoid lesions it is associated with a false-negative rate of 12%,[29] similar to that of double-contrast barium enema examination.[30] It may also fail to detect carcinoma in 10% of cases.[29] The procedure is not without complications. Perforation rates of 0.1% to 0.6% and bleeding rates of 2.2% to 4.7% have been reported.[29] Inability to reach the cecum ranges from 9% to 37%,[2,3,22,31,32] a serious limitation in view of the recently observed right-sided shift of neoplasia. It is also more costly, sedation is often necessary and the complication rate is higher than for the barium enema study.[25] However, it is superior in enabling direct inspection of the mucosa, thus having a false-positive rate of zero.[30] It can detect the so-called diminutive polyp, biopsy and destroy it using the cautery biopsy forceps. Although it can confirm the suspicion of anastomotic recurrence, the problem is now believed to begin extraluminally, before reaching the mucosa, a fact that is better appreciated on barium enema examination.[33] Taken together, barium enema and colonoscopy have a combined sensitivity approaching 100%.[30]

Although many studies have compared the efficacy of both procedures, they are not directly comparable; some have been conducted prospectively, others are retrospective. Periods of follow-up vary, and generally the conclusions reached are biased, depending on whether the author is an endoscopist or radiologist.

We believe that colonoscopy plays a valuable role in the follow-up of patients after resection for colorectal carcinoma, but we share the view of others[34,35] that the two examinations are complementary and that one should not be done to the exclusion of the other.

Another point needing clarification is the timing and frequency of colonoscopy. An apparent consensus is that it should be performed preoperatively since it enables synchronous polyps to be removed, neoplasms to be identified and modification of the planned operative procedure in 5% to 16% of cases.[22-24] Should obstruction, perforation or other mitigating circumstances prevent its performance preoperatively, then it should be done within the first 3 to 6 months after resection. Postoperative follow-up should be most intense in the first 2 years; the frequency of colonoscopy in this period is debatable. Despite the many suggestions on the subject in the literature, there is little conclusive evidence justifying the cost and risk of performing colonoscopy more often than annually during the initial 2 years after colorectal resection. This question can only be answered definitively by a long-term prospective study.

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Demographic and Medical Characteristics of Adult Head Injuries in a Canadian Setting

This study provides demographic and medical information about patients admitted with head injuries to Sunnybrook Medical Centre, Toronto, Ont., in 1978 and in 1982. Data are presented about patient age and sex, type and cause of accident, length of stay, extracranial complications, severity of head injury, frequency of use of various neurodiagnostic techniques and type of discharge placement. The costs of hospitalization for such patients, both in the Sunnybrook Medical Centre and for Canada as a whole, are estimated.

Cette étude révèle les données démographiques et médicales des patients qui ont été hospitalisés pour traumatisme crânien au Sunnybrook Medical Centre de Toronto, en 1978 et en 1982. Les données concernent l'âge et le sexe des patients, le type et la cause des accidents, la durée du séjour, les complications extracrâniennes, la gravité des blessures à la tête, la fréquence d'utilisation des diverses techniques neurodiagnostiques et le type de placement lors du congé. On évalue les coûts d'hospitalisation de ces patients, au Sunnybrook Medical Centre et pour l'ensemble du Canada.

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The frequency of head injury is substantial and the problem is associated with a correspondingly high cost to society. Approximately 50 000 patients are discharged from Canadian hospitals annually with a diagnosis of either skull fracture or intracranial injury.[1] It has been estimated that there are between 20 000 and 30 000 serious head injuries in Canada each year.[2] In 1983, over 3400 deaths were attributed to such injuries.[3]

Although the exact economic costs of head injury to Canadian society are not known, statistics from the United States give some idea of their potential magnitude. In 1974, the total direct and indirect economic costs of head injury in the US were estimated at over $2.3 billion.[4] If that figure is adjusted to reflect population differences between the two countries, then the equivalent costs to Canadian society at that time would have been approximately $230 million. Recently, Ivan[2] has estimated that the current cost to Canada of head trauma is $4 billion a year. Although these two figures differ substantially, even the lower figure represents substantial economic costs to Canada.

In spite of its importance as a health care problem, relatively few studies have investigated adult head injuries in Canadian settings. Klonoff and Thompson[5] reviewed the incidence of head injuries in individuals over the age of 16 years who were either seen in the emergency department of Vancouver General Hospital or admitted to that hospital in 1967. Their data indicated a preponderance of injuries for men and a higher incidence among younger adults. Twice as many men as women were admitted to hospital. The single greatest cause of head injury was motor vehicle accidents (39.6%) with falls being the next most frequent cause (19.3%).

Nelson and colleagues[6] studied the epidemiology of head injuries among patients admitted to the Trauma Unit at Sunnybrook Medical Centre from Apr. 1, 1981 to Dec. 31, 1982. Over two-thirds of the patients admitted were classified as head injured. Over 80% of these injuries were the result of motor vehicle accidents or pedestrian-motor vehicle accidents. In this study also there were more than twice as many men as women. Nelson's patients were younger than those in Klonoff's study, with over 70% being less than 41 years old. The death rate was greatest in those over the age of 60 years; in that group one of every four patients admitted with head injuries died.

Parkinson and associates[7] studied 3000 consecutive patients with head injury admitted to the Health Sciences Centre in Winnipeg. Unlike the previous studies, children were included. Again there was a predominance of males and younger patients. Their sample also showed almost as many falls (873) as traffic-related injuries (988), a finding that is probably attributable to the inclusion of children. In their setting, 35% of the head injuries were sustained in fights or assaults compared with 12.9% in the study of Klonoff and Thompson[5] and 1.5% in that of Nelson and colleagues.[6]

One striking aspect of the existing epidemiologic literature has been the lack of a consistent definition of head injury across the studies. Klonoff and Thompson[5] did not specifically define their criteria for head injury but did include patients with injuries to the scalp alone, while both Nelson and colleagues[6] and Parkinson and associates[7] excluded these injuries. Parkinson's group also did not define clearly their criteria for calling patients head injured. These two studies included only patients who were hospitalized, but Klonoff and Thompson[5] also in-

cluded patients seen only in the emergency department. Nelson's group included only those patients who had either computed tomographic evidence of brain lesion, loss of consciousness or post-traumatic amnesia, and their sample included only patients who were admitted to the Trauma Unit; other head-injury admissions to Sunnybrook Medical Centre were not included.

The absence of common diagnostic criteria makes it difficult to compare the results from these different studies. One possible way to assure greater diagnostic consistency across settings would be to use the International Classification of Diseases (ICD-9).[8] While there are some problems classifying head injuries by this system,[9,10] it at least provides some basis for consistency of definition across settings.

A second problem with previous Canadian studies has been a lack of information about the severity of the injury. Different criteria have been used and, in some cases, scant attention has been paid to the issue of severity. The Glasgow Coma Scale (GCS)[9] has gained increasing acceptance as a quantitative index of the severity of head injury. Providing GCS scores would permit researchers to compare severity of injuries across samples.

Bearing in mind the limitations of the existing literature, we designed a study to provide data on a sample of head-injured individuals whose diagnoses were based on ICD-9 criteria, with severity documented (where possible) by GCS scores.

Method

We reviewed the charts of patients who had been discharged (or died) with a diagnosis of closed head injury in either 1978 or 1982 at Sunnybrook Medical Centre in Toronto. Time of discharge was used because medical charts at this institution are coded and filed on the basis of date of discharge. Two different years were chosen in the hope that this approach would provide some estimate of the stability of the findings over time.

Between 1978 and 1982, two major changes occurred in the evaluation of head-injured patients treated at our hospital. First, the hospital did not acquire its first computed tomography scanner until September 1978. Before then, computed tomograms were obtained at other hospitals, so fewer computed tomograms were available for 1978. Second, GCS scores were not routinely obtained on patients admitted in 1978, but this practice had changed by 1982.

Table I—ICD-9 Diagnoses of Patients Included in Present Study

Fractures
800 Fracture skull – vault
801 Fracture skull – base
803 Fracture skull – not specified
Intracranial injury (excluding those with skull fracture)
850 Concussion
851 Cerebral laceration and contusion
852 Hemorrhage – subarachnoid, subdural, extradural
853 Hemorrhage – other and unspecified, intracranial
854 Head injury – not specified

Table III—Type of Accident

Type	1978	1982
Motor vehicle	76	120
Pedestrian	15	21
Bicycle	4	4
Sports	16	17
Interpersonal violence	15	10
Fall	84	85
Hit by falling object	7	10
Unknown	2	1

Table II—Distribution of Patients by Age, Sex and Year of Discharge

	1978*		1982	
Age, yr	Males	Females	Males	Females
11 – 19	40	11	37	11
20 – 29	36	7	53	21
30 – 39	18	9	19	15
40 – 49	12	9	27	8
50 – 59	14	13	22	8
60 – 69	14	6	12	9
70 – 79	3	9	9	8
80 – 89	7	7	3	4
90 +	3	0	1	1
Totals	147	71	183	85
Mean age	36.7	47.7	36.6	42.4
SD	21.7	21.9	18.6	22.1

*1 patient missing because his age was not recorded.

Patients

Patients were included in the study only if their discharge diagnoses included one of the ICD diagnoses listed in Table I. Patients with fractures of the facial bones and those with superficial facial and scalp lacerations were excluded because they would not likely have brain dysfunction and our primary interest was in patients with potential brain injury. Using the ICD-9 criteria shown in Table I, we identified 219 cases for 1978 and 268 for 1982. There were an additional 19 charts for the 2 years that either could not be located or had a questionable diagnosis of head injury.

Findings

Data on patient age and sex by year of discharge are presented in Table II. The head-injured patients were relatively young, with a tendency for males to be younger than females. The mean age of the patients for 1978 and 1982 was 40.3 and 38.4 years respectively.

With respect to the type of accident, approximately 43% of the cases involved some form of motor vehicle accident (including bicycles) in 1978 (Table III). In 1982, this figure was 54%. In both years, the second most frequent cause of accident was a fall. Almost all the head injuries were of the closed type, 96.3% in 1978 and 98.1% in 1982. The death rate was 13% in 1978 and 15% in 1982.

Data on length of stay are presented in Table IV. In both years, over half of the patients were discharged within 2 weeks of admission.

The frequency of associated extracranial complications was high (Table V). Over 90% of the patients sustained multiple injuries. The number of patients who were admitted through the Trauma Unit increased from 63 (28.7% of the 1978 sample) to 122 (45.5% of the 1982 sample) between the study years.

Table IV—Length of Hospital Stay

Stay, d	1978	1982
1	62	38
2	19	20
3	6	10
4	7	8
5	12	14
6	5	6
7	6	8
8 – 14	38	50
15 – 28	24	49
29 – 56	24	37
57 – 84	8	17
> 84	8	11

Glasgow Coma Scale scores for 1982 are presented in Table VI. Using a cut-off score of 13 and above, we could classify approximately 50% of these injuries as mild. However, there was a large number (71) for whom complete scores could not be obtained. Since 73% of this group were intubated, they were probably among the more severely injured.

Table V—System Involved for Extracranial Complications

System	1978	1982
Musculoskeletal	76	111
Respiratory	33	87
Cardiovascular	12	19
Central nervous	143	220
Gastrointestinal	15	36
Genitourinary	13	30
Integumentary	154	187

Table VI—Glasgow Coma Scale (GCS) at Admission*

GCS	1982
3	6
4	3
5	2
6	7
7	1
8	2
9	7
10	5
11	6
12	17
13	33
14	100

*Glasgow Coma Scale scores were only infrequently recorded in 1978 and are therefore not reported here. In 71 patients a medical condition (e.g., intubation) precluded scoring. In 8 the score was not recorded.

Table VII—Type of X-ray Procedure

Procedure	1978	1982
Skull x-ray	192	131
Brain scanning	22	2
Tomography	7	10
Computed tomography (at Sunnybrook Medical Centre)	21	206
Echoencephalography	9	0
Angiography	31	6
Cerebrospinal fluid flow study	0	4
Isotope cisternography	2	0
Fluoroscopy	2	0

Table VIII—Discharge Placement*

Placement	1978	1982
Home	159	156
Convalescent care	8	12
General hospital	6	6
Rehabilitation centre	10	47
Chronic care	8	5
Extended care	2	2

*In 1978 there were 26 deaths and in 1982, 40.

Table VII addresses changes in the radiologic investigation of these patients over the 2 years in question. The impact of computed tomography is particularly noteworthy. Only 21 scans were done in 1978 at our institution, but by 1982 the number had reached 206. Although the number of patients increased between the 2 years, the only diagnostic procedures that showed an increase were computed tomography, tomography and studies of cerebrospinal fluid flow. Other data indicate that a higher percentage of the patients underwent monitoring of intracranial pressure in 1982 (18.6%) than in 1978 (1.4%).

An attempt was also made to determine the percentage of head injuries that might have been the result of suicide attempts. Patients were classified as such if the discharge summary and some correlative piece of information, such as the social worker's notes, made reference to this as a factor. With these criteria, the incidence was 2.7% in 1978 and 1.1% in 1982. However, since this was not a prospective study and since incidence figures for suicide are often underestimated,[11] our rates may be low.

Estimates were also made of the use of alcohol at the time of the accident. Patients were classified as using alcohol if this was reported in either the admission notes or discharge summary. If there was no such reference, the patient was classified as not using alcohol, even if there was a documented history of alcohol abuse. By these criteria, 24.6% of the 1978 patients and 17.5% of the 1982 patients showed signs of alcohol use at the time of their injury.

Table VIII presents information about the discharge placement of patients. In both years, the majority of patients were discharged home, but from 1978 to 1982, there was an increase in the percentage of patients admitted to rehabilitation institutions.

Discussion

Previous studies of the demographic characteristics of head-injured patients have found that victims are predominantly young males. Our study replicated these findings. In both years, there were approximately twice as many males as females and approximately two-thirds of the patients were under the age of 50 years. Head injury was most commonly caused by motor vehicle accidents, with the next most frequent cause being falls. In contrast to findings from some American studies, few injuries resulted from violence.

The severity of injuries seen in the present study is also similar to that reported in other investigations. For example, in one cooperative study of Glasgow Coma Scale scores in hospitals in Galveston and Houston,[12] it was found that 53% of such injuries fell in the mild range (that is, greater than 12). In the present study, 49.6% of the patients admitted in 1982 had GCS scores in this range.

It is apparent that there are some differences in the findings obtained between the 2 years surveyed in this study. There were more admissions to hospital in 1982 and a higher percentage of these admissions came through the Trauma Unit. Lacking GCS scores from 1978, one cannot conclude that the injuries in 1978 were less severe than those seen in 1982, but given the increase in percentage (and number) of Trauma Unit admissions, it is possible that there has been some change in the types of injuries sustained by those admitted.

One of the clearest changes between 1978 and 1982 was the increase in intracranial pressure monitoring. The impact that computed tomography has had on the use of other radiologic procedures is also clearly demonstrated.

The death rates noted here indicate that many of the patients were severely injured. The percentage of deaths is similar to that reported by Nelson and colleagues[6] (16%) and Klonoff and Thompson[5] (13.6%). Parkinson and associates[7] reported a rate of 4.4%, but their sample contained a high incidence of interpersonal violence and may, therefore, not have comprised injuries as severe as in other settings.

This study also suggests that the average person admitted to our hospital with cerebral injury is likely to have involvement of some other body system. In both years about 70% of the patients had at least one body system other than the central nervous system involved. While some of these injuries may have been minor (such as skin abrasions and lacerations), others were not. Recently, there has been substantial research on the psychosocial problems associated with head injury. While the effects of head injury should not be underestimated, these problems may be a function not just of the head injury but also of all the other injuries sustained. Indeed, there is some evidence that the psychosocial sequelae in trauma patients with and without head injury do not

differ,[13] suggesting that head injury does not have a unique psychosocial impact.

This study also provides a basis for estimating some of the economic impact of head injury. In 1978, the estimated average cost of a day's stay in our hospital (exclusive of physician's fees and direct bills to the provincial health plan) was $215. (This represents the *average* cost to the hospital of a day's stay by the *average* patient. The average cost of care for head-injured patients may be higher.) By 1982 this figure had risen to $320/d. Thus, the direct costs of hospitalization for head-injured patients in this hospital were approximately $767 000 for the year 1978. The estimated costs for 1982 had risen to $2.1 million or, alternatively, approximately $7836 per patient. Statistics Canada figures for 1980–1981[1] give an average length of hospital stay of approximately 8.3 days (versus 24.5 days in our setting) for the average patient over the age of 15 years with either a skull fracture or a head injury. If the annual Canadian incidence of 50 000 patients a year is multiplied by 8.3 days, and the resulting figure is multiplied by a cost of $320/d, then the hospital cost of head injury would be $132.8 million. This figure, of course, excludes physician's and surgeon's fees, post-hospital care and income loss.

While the current study gives some idea of various demographic characteristics as well as of the medical and surgical treatment of head-injured patients, there is clearly a need for further research on this topic. For example, there is a need for replication in other Canadian settings to determine more precisely how much variation there is across settings in the type and severity of such injuries. This is one area in which the use of standardized diagnostic criteria (such as the ICD-9) and standardized criteria for severity (such as the GCS) can be useful. Our study also suggests that there have been some changes, even over the relatively brief period of the present study, in the ways in which head injury is investigated and treated. It is therefore important to have regular reviews of the care of head-injured people in Canada.

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SESAP V Critique

ITEM 112

Overwhelming postsplenectomy sepsis (OPSI), recognized since 1952, highlights the importance of preserving the spleen for prevention of OPSI. Progression from health to death frequently occurs in a matter of hours. Patients who have had splenectomy should be informed about the importance of reporting even minor respiratory and other infections promptly. Most fatal sepsis occurs in the first two years after splenectomy, but it has been reported many years later.

Pneumococci have been isolated in approximately 50% of the cases. Polyvalent pneumococcal vaccine gives some protection, but not all of the types of *Pneumococci* involved are included in the vaccine. Aggressive treatment of all infections in these patients is therefore still necessary. The incidence of OPSI among trauma victims who have had splenectomy is much lower than that among patients who have had the splenectomy for hematologic disease.

Although accessory spleens or the development of splenosis (autoimplantation of fragments of spleen) might provide protection against OPSI, fatal sepsis has been reported after both.

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Preservation of the Spleen Using Human Fibrin Seal

Because of the spleen's role in host defence and the recognition of overwhelming post-splenectomy sepsis, the current aim of treatment for splenic injuries is to preserve the spleen. A number of hemostatic agents have been used in an effort to control bleeding but have not proved satisfactory. The authors report the results of an experiment using a two-component fibrin seal on injured rabbit spleens.

In female rabbits a longitudinal laceration of the entire spleen was made. After 2½ minutes of continuous hemorrhaging, the spleens were either not treated (5 rabbits) or treated by splenectomy (5), suture repair (10) or fibrin-seal repair (10). Hemoglobin values were measured preoperatively and 3 days postoperatively.

The greatest number of deaths within 14 days occurred in the untreated group. There was no difference in death rate between the treated groups; similarly, there was no difference in blood loss or fall in hemoglobin values. Fewer adhesions formed in the fibrin-seal group than in the others ($p < 0.02$). Histopathological examination revealed a greater fibrinoblastic response in the spleens treated with fibrin seal than in the other groups.

The authors believe that fibrin seal is an effective and safe hemostatic agent applicable to splenic parenchymal injuries, and that it promotes wound healing and suppresses adhesion formation.

A cause du rôle important de la rate dans les mécanismes de défense immunitaire et puisque l'on connaît bien le risque de sepsie fulminante post-splénectomie, le traitement actuel des lésions spléniques vise à conserver la rate. Quelques agents hémostatiques ont été utilisés pour tenter de juguler l'hémorragie mais aucun ne s'est avéré satisfaisant. Les auteurs décrivent les résultats d'une expérience au cours de la quelle un adhésif de fibrine à deux constituants fut utilisé sur des rates lésées de lapin.

Chez des lapines, une lacération longitudinale fut pratiquée sur toute la longueur de la rate à l'aide d'un scalpel no. 10. Après 2½ minutes d'hémorragie continue, la rate fut soit laissée sans traitement (5 lapines), traitée par splénectomie (5), réparée par suture (10) ou réparée à l'aide de l'adhésif de fibrine (10). L'hémoglobinémie fut mesurée en préopératoire et 3 jours après l'opération.

Le plus grand nombre de décès à survenir au cours des 14 jours d'observation fut enregistré au sein du groupe non traité. On n'a observé aucune différence de taux de mortalité entre les groupes traités. De même, il n'y a eu aucune différence entre les traitements en ce qui concerne la perte sanguine et la chute de l'hémoglobinémie. L'adhésif de fibrine a causé moins d'adhésions que les autres traitements ($p < 0.02$). L'examen histopathologique a révélé une réponse fibrinoblastique plus importante dans les rates traités avec l'adhésif de fibrine que dans les autres groupes.

Les auteurs croient que l'adhésif de fibrine est un hémostatique sûr et efficace qui se prête au traitement du parenchyme splénique en favorisant la cicatrisation et en supprimant la formation d'adhésions.

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Historically, the treatment of choice for the ruptured spleen has been splenectomy.[1] However, with increasing knowledge of the spleen's role in host defences and recognition of the entity of overwhelming post-splenectomy sepsis,[2,3] enthusiasm for retaining splenic tissue has become widespread.[4–6]

Procedures such as splenorrhaphy, once discarded, are now accepted methods for managing splenic trauma. However, splenic preservation must be proven to be as safe as splenectomy and to minimize the risk of fulminant sepsis.

Attempts to salvage the spleen have included the use of partial splenectomy, splenic suture, splenic artery ligation, the application of hemostatic agents and no treatment. In addition, splenic autotransplantation has been performed.

A variety of topical hemostatic agents have been used to control splenic surface bleeding (e.g., Avitene, Gelfoam) but these agents have not been entirely satisfactory.[7,8]

This study examines the use of highly concentrated human fibrinogen as a hemostatic agent in splenic injury.

Material and Methods

The two-component fibrin seal simulates the physiologic process of wound closure. Its mode of action is based on the central function of fibrin in blood coagulation, creating a hemostatic clot.

The major ingredients of this two-component adhesive are fibrinogen and thrombin solutions. The fibrinogen solution contains fibrinogen, Factor XIII, fibronectin, calcium plasminogen and aprotinin. The thrombin solution contains thrombin and calcium chloride. When the two solutions are mixed, fibrinogen is transformed to fibrin monomers which aggregate to form a gel. Concomitantly, thrombin acts upon Factor XIII and, in the presence of calcium, Factor XIIIa is formed. This factor cross-links the

fibrin monomers to form a high-molecular-weight polymer. Cross-links between the fibrin polymer and the collagen of the tissue to which the sealant was applied are also formed.

In the course of wound healing, plasminogen activators convert plasminogen to plasmin. The cross-linked fibrin is lysed into fibrin degradation products. This process is retarded by the antifibrinolytic agent aprotinin.

Thirty female rabbits, each weighing between 2.2 and 2.6 kg and fed a water and pellet diet, were anesthetized with intravenous sodium thiopental. Under sterile conditions, a midline laparotomy was performed on each rabbit and the spleen mobilized. A no. 10 scalpel blade was used to create a longitudinal laceration down the entire length of the spleen. The spleen was then observed for 2½ minutes, during which time the wound did not stop hemorrhaging.

Animals were randomized into four groups: splenectomy (5 rabbits), suture repair (10), fibrin-seal repair (10) and no repair (5).

In the suture and fibrin-seal repair groups, splenectomy was performed if the repair failed to control the hemorrhage.

The abdominal incisions were closed in two layers with 2-0 silk sutures, and the animals were allowed to recover in warm surroundings.

All blood losses were carefully measured. Blood samples were obtained preoperatively and on postoperative day 3 for a complete blood count. The animals were then explored again on postoperative day 14 or within 24 hours of death. Careful note was made of adhesion formation, and the spleens were removed for histopathological examination.

Statistical analysis was performed with Student's paired *t*-test, analysis of variance and Duncan's multiple range test.

Results

Of the animals that had no repair, two (40%) died. None of the animals that underwent splenectomy alone died, but one that had suture repair did. In the fibrin-seal group none died, although one animal required splenectomy because of a hilar vessel injury (Fig. 1).

Blood loss for the animals that underwent splenectomy or splenorrhaphy did not differ significantly (Fig. 2). Those that underwent splenectomy lost an average of 6.8 ml compared with 6.2 ml and 7.0 ml for those that underwent suture repair and fibrin-seal repair, respectively.

The decrease in hemoglobin concentration did not differ significantly between groups (Fig. 3); however, the decrease within each group was significant ($p < 0.05$).

The platelet counts were also evaluated pre- and postoperatively. There was no significant difference between the splenectomy and the suture-repair group, but between these two and the fibrin-seal-repair groups, the change was significant ($p < 0.05$) (Fig. 4).

At autopsy the rabbits that did not undergo splenectomy or splenorrhaphy and survived 14 days all had extensive adhesions. The animals that died had blood within the peritoneal cavity.

Adhesions formed in 60% of the animals that had splenectomy and in 50% of those with suture repair but in only 20% of those with fibrin-seal repair ($p = 0.02$ compared with no repair, splenectomy and suture repair) (Fig. 5).

Histopathological examination of the spleens repaired with the fibrin seal showed an intense inflammatory

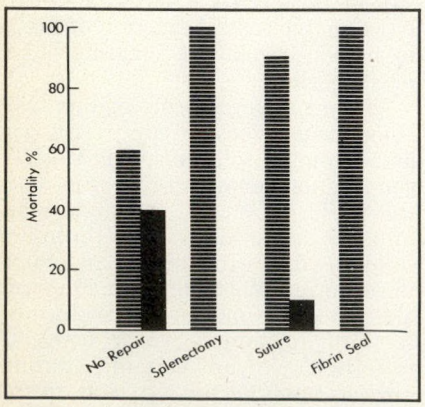

FIG. 1 — Mortality by group. Hatched bars = alive, black bars = dead.

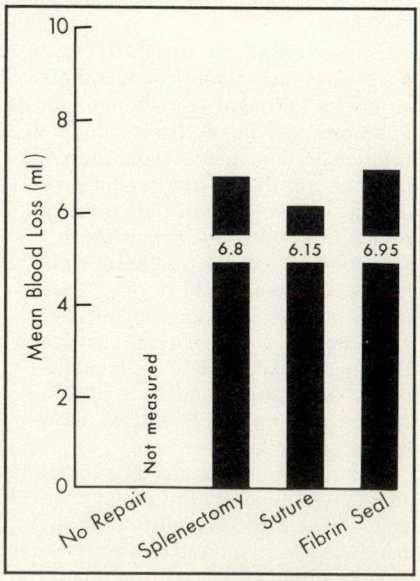

FIG. 2 — Blood loss by group.

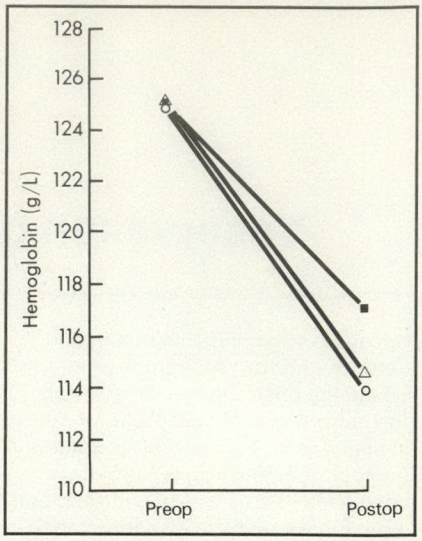

FIG. 3 — Change in hemoglobin level by group. ■ = splenectomy, ○ = suture, △ = fibrin seal.

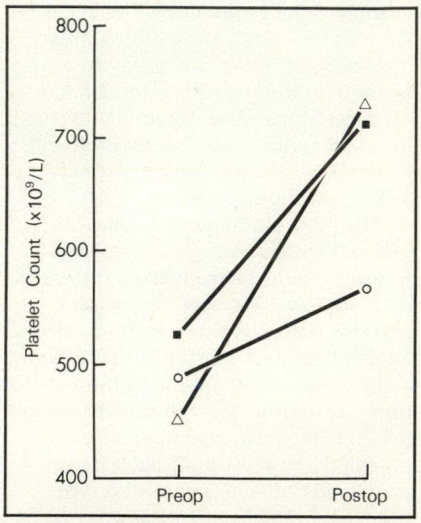

FIG. 4 — Change in platelet count by group. ■ = splenectomy, ○ = suture, △ = fibrin seal.

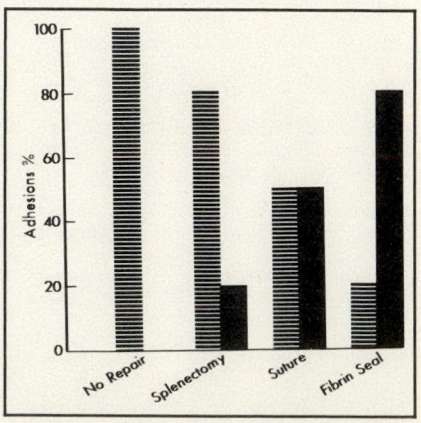

FIG. 5 — Adhesion formation by group. Hatched bars = yes, black bars = no.

reaction at the spleen–fibrin seal interface. A great number of fibroblasts were present, indicating an effective wound healing process. In spleens without fibrin seal, wound healing was also seen, but the reaction was less intense with fewer fibroblasts.

Discussion

Because of increasing recognition of the spleen's role in immunologic function, the principle of preservation is now firmly implanted in surgical practice. The risks and benefits of attempting splenic preservation, however, must be weighed against those of splenectomy.

In children, the incidence of sepsis after a normal spleen has been removed because of injury ranges up to 6% and the death rate up to 73%.[9] There is little question that the benefits of splenic preservation outweigh the risks.

In adults, though, the overall mortality of an isolated splenic injury requiring splenectomy is less than 0.5%, and the incidence of post-splenectomy sepsis is significantly less than that in children.[10]

Any attempt to preserve the spleen must yield results superior to the risks involved with splenectomy and delayed post-splenectomy sepsis.

Approaches to preservation of a damaged spleen include observation without operation, reimplantation of splenic tissue and splenic repair. The nonoperative approach has been used successfully in children, but the safety of this method in adults is controversial. In one series,[11] 73% of patients initially managed nonoperatively later required surgery.

When the spleen cannot be repaired because it is too badly injured, splenic reimplantation has been performed to preserve splenic tissue. It has been shown experimentally and clinically that reimplanted splenic fragments will restore a number of functional parameters lost after splenectomy. However, there is no proof that return of these areas of function correlates with a reduced risk of overwhelming post-splenectomy sepsis. In addition, uptake of radionuclides does not correlate with immunologic function. Splenic mass and blood flow seem to be the crucial factors. This method of splenic autotransplantation, therefore, remains investigational.[12,13]

A direct attack on the bleeding site appears to be the best approach for splenic salvage. This includes splenic artery ligation, splenic suture, partial splenectomy, application of hemostatic agents or combinations of them.

The fibrin seal can be used as the primary hemostatic agent, or as an adjuvant in managing the traumatized spleen, without increasing the perioperative morbidity or mortality and without increasing the incidence of delayed hemorrhage.

Injuries to the hilar vessels of the spleen are not amenable to conservative management and should be treated by splenectomy. However, for splenic parenchymal injuries, fibrin seal gives rapid and adequately hemostatic repair. For these injuries, sutures may not be required, thereby reducing further trauma and maximizing the amount of viable tissue remaining. Fibrin seal also has the theoretical advantage of being effective for a pre-existing coagulopathy, because of the direct application of components of the coagulation system to the wound.

Fibrin seal seems to evoke less peritoneal inflammatory response than other agents, as evidenced by the lack of adhesion formation. Histologically, however, there is an intensive inflammatory response with respect to tissue reactivity. Fibrin seal evokes an increased fibroblastic response in the tissue–fibrin seal interface. There is some evidence to suggest that fibrin and Factor XIII stimulate fibroblast growth within the injured organ, promoting wound healing.[14]

The use of the fibrin seal, therefore, appears to be a safe and effective method for repairing splenic parenchymal injuries. Maximum preservation of splenic tissue is achieved with no increased risk of delayed hemorrhage. Further studies of splenic function require evaluation.

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Dalacin® C Phosphate Sterile Solution

(clindamycin phosphate)

Antibiotic

Recommended Applications

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

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

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

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

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 occuring up to several weeks post-therapy should be managed as if antibiotic-associated.

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

Studies indicate a toxin(s) produced by Clostridia (especially Clostridium difficile) may be a principal cause of clindamycin and other antibiotic-associated colitis. These studies also indicate that this toxigenic Clostridium is usually sensitive *in-vitro* to vancomycin. When 125 mg to 500 mg of vancomycin were administered *orally* four times a day for 5 - 10 or more days, there was a rapid observed disappearance of the toxin from faecal samples and a coincidental recovery from the diarrhea.

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

Precautions: Dalacin C Phosphate (clindamycin phosphate), like any drug, should be prescribed with caution in atopic individuals. Dalacin C Phosphate must be diluted for intravenous administration. (See Dosage and Administration)

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

As with all antibiotics, 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 absesses.

(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 conjuction with the use of indwelling I.V. catheters and it is difficult to know how much the drug contributed to the irritation. Two patients developed localized erythema, swelling and pain at the site of the infusion.

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

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

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

** Due to underlying myocarditis in this patient.

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

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

DOSAGE AND ADMINISTRATION

Adults

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

Intravenous Administration: Dalacin C Phosphate (clindamycin phosphate) must be diluted prior to I.V. administration to a dilution of 300 mg in 50 mL of diluent (6mg/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.

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.

Product Monograph available upon request.

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A Review of Intra-articular Knee Injuries in Racquet Sports Diagnosed by Arthroscopy

Because of the recent rapid increase in the number of knee injuries related to racquet sports, the authors undertook a retrospective study of such injuries seen over a 5-year period at the Toronto Western Hospital Sports Medicine Institute. The 121 patients who presented over the study period with a racquet-sports-related knee injury requiring arthroscopy represented 30% of all racquet-sports related injuries seen during that period. The mean age at presentation was 32.8 years and two-thirds of the patients were men. All the major racquet sports were represented. In all, 213 lesions (7 bilateral) were seen at 128 arthroscopies, and 165 arthroscopic procedures were performed. The most common lesion was meniscal followed by chondromalacia patellae, anterior cruciate ligament tears, chondral lesions and pathologic plicae. Over 90% of the patients returned to their chosen racquet sport within 3 months of the arthroscopy and most were playing at a similar performance level to that before the initial injury.

Devant l'augmentation rapide et récente du nombre de blessures du genou reliées aux sports de raquettes, les auteurs ont entrepris une étude rétrospective des blessures de ce type qui ont été vues au cours d'une période de 5 ans au Toronto Western Sports Medicine Institute. Les 121 patients qui ont été reçus au cours de cette période souffrant d'une blessure du genou reliée aux sports de raquettes et nécessitant une arthroscopie représentaient 30% de toutes les blessures dues aux sports de raquettes vues durant la même période. L'âge moyen était de 32.8 ans et deux-tiers des patients étaient des hommes. Tous les principaux sports de raquettes étaient représentés. Au total, 213 blessures (dont 7 bilatérales) ont été observées au cours de 128 arthroscopies, alors que 165 interventions arthroscopiques étaient pratiquées. Les blessures les plus fréquentes affectaient les ménisques, suivies des chondromalacies rotuliennes, des déchirures du ligament croisé antéro-externe du genou, des lésions du cartilage et des replis pathologiques. Plus de 90% des patients sont retournés à leur sport de raquette préféré moins de 3 mois après l'arthroscopie et la plupart jouait au même niveau de compétition qu'avant leur blessure.

Participation in racquet sports has escalated rapidly over the past 10 years. The United States Squash Association estimates that there are more than 500 000 people playing squash in that country, with the number increasing at a rate of more than 20% annually.[1] Racquetball is the fastest growing racquet sport in North America with more than 10 million people now playing,[2] and tennis is as popular as ever. Despite this increase in participation and a concomitant increase in the number of associated injuries, there is little information in the literature on the injury profile seen in racquet sports.[3-5] The literature that does exist addresses the problems of facial and upper extremity injuries but virtually ignores the lower extremity. Over the past year we have seen a lot of injuries to the lower extremity, especially to the knee, related to racquet sports. This prompted us to undertake a retrospective analysis of racquet-sports related injuries, with particular attention to knee injuries requiring arthroscopy, seen over a 5-year period (1982 to 1987) at the Toronto Western Hospital Sports Medicine Institute.

Patients and Methods

Of 404 racquet-sports related injuries seen, 222 (55%) involved a knee joint and 121 (30%) knees required arthroscopic evaluation based on the history of the injury and the physical findings. The injuries in these 121 patients were analysed by review of the patient's chart and by detailed questionnaire with telephone follow-up to form an epidemiologic profile in addition to accurate operative data. All patients were contacted. Although a formal follow-up might have provided more information, this was not possible for the majority of patients because many were from out of town.

Average follow-up was 27.2 months (range from 6 to 78 months). Several patients were followed up for less than 2 years, but since no strong conclusions are to be made based on the results of treatment, this should not be considered a major weakness of our study.

Findings

Two-thirds of the patients were male, ranging in age from 14 to 68 years (mean 32.8 years). All patients suffered an acute knee injury during participation in a racquet sport. Although several of these patients participated in other sports and had previous injuries, they were only considered for this study if it was clear that the injury was caused while playing a racquet sport. Two-thirds were injured playing squash or tennis, the remainder playing badminton or racquetball (Table I). Competition level of the injured participants ranged from recreational beginner to professional, but over 90% of those injured were of an advanced amateur level of participation, playing at least twice a week.

Warm-up

Pre-game preparation and surface conditions were considered as possi-

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ble factors in the injuries and were therefore investigated in detail. In over 60% of the patients the warm-up procedure was inadequate; either there was no warm-up at all or inadequate time was given to stretching exercises or rallying. Of the remainder, 22 patients (18%) performed at least 5 minutes of rallying and 25 (21%) engaged in a warm-up procedure that included at least 10 minutes of slow, prolonged stretching followed by at least 5 minutes of rallying before competition. The surface played on varied depending on the sport. The condition of the playing surface was normal in the majority of cases. However, a small group of patients reported playing on either hard, slippery or irregular surfaces.

Previous Injury

In response to questioning about previous injuries, most patients reported none, but 22 had at least one prior knee injury, including 14 meniscal tears, 9 medical collateral ligament sprains, 7 cases of patellar tendinitis and 2 anterior cruciate ligament tears. Seventeen of the patients had suffered ankle injuries in the past.

Mechanism of Injury

Over 85% of the patients injured their knee through a twisting mechanism, either by a fast turn for a difficult shot, an improper landing after playing a high overhead shot, or as a result of fast stop or start (Table II). Twisting places rotatory forces on the knee joint and commonly leads to intra-articular injuries. In a small group of patients, direct contact with a wall, the racquet or, on one occasion, a player, resulted in the injury to the knee joint.

Symptoms

Time from injury to presentation ranged from immediately to more than 6 months (Table III). Almost 50% presented within 2 weeks and over 90% within 3 months. In all cases the patient's symptoms at presentation were referable to the injury and were not simply exacerbations of previous injuries. The most common complaint upon presentation was of knee pain (over 90%). Other symptoms included intermittent swelling (62%), a feeling of instability (27%) and frank giving way (8%). These symptoms, combined with the findings of joint line or patellofemoral tenderness, joint effusion or ligamentous instability (demonstrated by anterior drawer, Lachman and pivot shift signs), led to the arthroscopic evaluation.

Arthroscopy

Of the 121 patients, 114 underwent a unilateral arthroscopy and 7 bilateral – 128 arthroscopic examinations in all. A total of 202 intra-articular lesions were found, indicating that in most cases more than one lesion was present (Table IV).

Five major categories of lesions were found at arthroscopy. The most common was meniscal lesions (76 cases [60% of knees]). This preponderance is likely related to the mechanism of injury (i.e., twisting) reported by most patients. The other categories were chondromalacia patellae (32 cases [25% of knees]), anterior cruciate ligament injuries (28 cases [22% of knees]), chondral lesions (26 cases [20% of knees]) and pathologic plicae (15 cases [12% of knees]). Other intra-articular lesions found included osteoarthritis, loose bodies, fat-pad contusions and traumatic synovitis. Eleven arthroscopies revealed no intra-articular lesions. Thus, in over 90% of knees subjected to arthroscopy, one or more lesions were found, and in all cases the condition correlated with the patient's clinical presentation. Meniscal tears, the most common lesion, can be classified by type (Table V). Almost 50% of the meniscal tears were of the oblique or flap type. Vertical longitudinal tears, commonly known as bucket handle tears, and vertical transverse tears, commonly known as radial tears, made up the bulk of the rest. Medial meniscal tears far outnumbered lateral tears, and the posterior horn was the most common site of injury within the meniscus. These numbers correlate well with those reported in the literature.[6]

From the data presented one might consider the chronicity of the disease process seen arthroscopically. As already noted, most patients had more than one lesion or diagnosis. In all cases of potentially degenerative disease (i.e., osteoarthritis or late-stage chondromalacia), there was a more acute problem as well (meniscal tear, chondral lesion or fat-pad contusion). It should also be remembered that the patients all had injuries referable to a racquet sport in the recent past to account for their acute condition.

A wide variety of arthroscopic surgical procedures were performed to treat these intra-articular lesions (Table VI). Of 165 procedures, there were

Table I—Racquet Sports Participation

Sport	No. (%)
Squash	43 (36)
Tennis	38 (31)
Badminton	25 (21)
Racquetball	15 (12)

Table II—Mechanism of Injury

Mechanism	No. (%)
Twisting	108 (89)
Improper landing	40
Fast turning	61
Fast stop	4
Fast start	3
Direct contact	6 (5)
Opponent	1
Wall	3
Racquet	2
Other	7 (6)

Table III—Time From Injury to Presentation

Time	No. (%)
0 – 1 wk	38 (31)
1 – 2 wk	19 (16)
2 – 4 wk	29 (24)
1 – 3 mo	23 (19)
3 – 6 mo	8 (7)
> 6 mo	4 (3)

Table IV—Arthroscopic Findings (202 Lesions)*

Findings	No. (%)
Meniscal lesions	76 (38)
Chondromalacia patellae	32 (16)
Anterior cruciate ligament lesions	28 (14)
Chondral lesions	26 (13)
Pathologic plica	15 (7)
Osteoarthritis	7 (3)
Miscellaneous (including loose bodies, fat-pad contusions, subluxating patella)	18 (9)

*Nothing found in 11 knees.

Table V—Type of Meniscal Lesions (n = 76)

Type of lesion	Medial	Lateral	Total (%)
Oblique (flap or "parrot beak")	28	8	36 (47)
Vertical longitudinal (bucket handle)	16	0	16 (21)
Vertical transverse (radial)	6	4	10 (13)
Multiple-plane (degenerative/complex)	6	2	8 (11)
Horizontal	2	0	2 (3)
Miscellaneous (discoid, hypermobile, meniscal cyst)	3	1	4 (5)

61 soft-tissue resections, mainly to meniscal lesions, 40 shavings of the articular cartilage of the patella or the femoral condyle and 33 lavage procedures. Trimming was considered to be the minimal resection in treating small meniscal tears. Débridement of articular cartilage of the femoral condyle was performed on five occasions. Only 11 knees required open operative procedures, including reconstructive procedures for anterior cruciate ligament deficiency and open meniscectomies for difficult posterior horn tears to the lateral meniscus.

Other therapeutic modalities were used in the pre- and post-arthroscopic management period. Oral anti-inflammatory agents have been shown to reduce post-arthroscopy swelling and pain, allowing earlier, more-effective rehabilitation.[7] Stretching exercises, ice, frictional massage and electrotherapy were all used. In several patients with anterior cruciate ligament tears the knee was braced.

Return to Sport

Most patients (91%) returned to their sport within 3 months of their arthroscopy (range from 1 week to 6 months) and achieved a performance level similar to that before injury (Table VII). Patients with meniscal lesions, chondral lesions or pathologic plicae tended to return more quickly, most within 3 months, whereas those with chondromalacia patellae or anterior cruciate ligament injuries generally had a more prolonged recovery. Eleven patients were unable to return to their sport as a result of their injury.

Table VI—Arthroscopic Surgical Procedures (n = 165)

Procedure	No. (%)
Resection	61 (37)
Meniscal	51
Plica	10
Articular cartilage shaving	40 (24)
Patella	19
Medial femoral condyle	18
Lateral femoral condyle	3
Lavage	33 (20)
Trimming	10 (6)
Meniscal	8
Fat pad	2
Débridement	8 (5)
Closed lateral release	3 (2)
Miscellaneous	10 (6)
Lateral substitution over the top	6
Open meniscectomy	3
Chondroplasty	1

Table VII—Return to Sport

Time, mo	No. (%)
0 – 1	30 (25)
1 – 3	55 (45)
3 – 6	20 (17)
> 6	5 (4)
No return	11 (9)

Discussion

In the past, emphasis has been placed on facial and upper extremity injuries in racquet sports. It is evident from this study that a substantial number of racquet sports injuries occur in the lower extremities, particularly knee joints. Over half the patients with knee injuries underwent arthroscopy and in 90% of those 121 people, gross intra-articular lesions were found. The lesions seen were no different from those seen in other sports injuries, and the proportions of lesions were similar to those in other non-contact sports. Investigations into the causes of the injuries identified twisting as the major culprit, but no strong conclusions can be made with respect to causative or preventive factors. It is our opinion that a proper warm-up, consisting of stretching and rallying for an adequate length of time, might reduce the number of injuries seen. Prospective, well-controlled studies into these and other potential preventive measures such as shoe type and condition are needed, so that appropriate recommendations can be made to the ever-growing number of racquet sports participants. The increasing use of protective equipment to prevent eye injuries by squash and racquetball players is indicative of the influence work such as this can exert. It was reassuring that over 90% of patients returned to their sport and that 80% returned within 3 months and had regained their pre-injury performance level. Just as other investigators have found in the past,[8,9] we believe that the use of operative arthroscopy, as opposed to more traditional open techniques, played a major role in the early and successful return of our patients to their desired activities.

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BOOKS RECEIVED

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The Clinical Management of the Renal Transplant Recipient With Cyclosporine. Edited by Ronald M. Ferguson and Bruce G. Sommer. Grune & Stratton, Inc., Orlando, Fla.; W.B. Saunders Company Canada Limited, Toronto, 1986. $88.25. ISBN 0-8089-1823-0.

Hair Transplantation. 2nd edition. Edited by Walter P. Unger and Rolf E.A. Nordström. 768 pp. Illust. Marcel Dekker, Inc., New York, 1988. $125.00 (US). ISBN 0-8247-7724-7.

Medical Management of the Surgical Patient. 2nd edition. Edited by Michael F. Lubin, H. Kenneth Walker and Robert B. Smith III. 707 pp. Illust. Butterworth Publishers, Stoneham, Mass., 1988. $54.95 (US). ISBN 0-409-95168-4.

Microsurgery in Trauma. Edited by William W. Shaw and David A. Hidalgo. 407 pp. Illust. Futura Publishing Company, Inc., Mount Kisco, NY, 1987. $87.50 (US). ISBN 0-87993-282-1.

Neural Blockade in Clinical Anesthesia and Management of Pain. 2nd edition. Edited by Michael J. Cousins and Phillip O. Bridenbaugh. 1171 pp. Illust. J.B. Lippincott Company, Philadelphia, 1988. $149.50 (US). ISBN 0-397-50562-0.

Operative Neurosurgical Techniques: Indications, Methods and Results. 2 volume set. Edited by Henry H. Schmidek and William H. Sweet. 1601 pp. Illust. Grune & Stratton, Inc., New York; W.B. Saunders Company Canada Limited, Toronto, 1982. $436.75. ISBN 0-8089-1439-1.

Reoperative Arterial Surgery. Edited by John J. Bergan and James S.T. Yao. 620 pp. Illust. Grune & Stratton, Inc., Orlando, Fla.; W.B. Saunders Company Canada Limited, Toronto, 1986. $147.50. ISBN 0-8089-1789-7.

Surgery Annual: 1988. Volume 20. Edited by Lloyd M. Nyhus. 372 pp. Illust. Appleton & Lange, East Norwalk, Conn., 1988. $69.95 (US). ISBN 0-8385-8728.

Trauma, Sepsis, and Shock. The Physiological Basis of Therapy. Edited by George H.A. Clowes, Jr. 587 pp. Illust. Marcel Dekker, Inc., New York, 1988. $125.00 (US). ISBN 0-8247-7502-3.

BOOK REVIEWS

BURNS AND THEIR TREATMENT. 3rd ed. I.F.K. Muir, T.L. Barclay and J.A.D. Settle. 177 pp. Illust. Butterworth and Co. (Publishers) Ltd., London; Butterworth Publishers, Stoneham, Mass., 1987. $65.00 (US). ISBN 0-407-00333-9.

Muir and Barclay are joined by J.A.D. Settle to produce the third edition of *Burns and Their Treatment*. Comparison of this edition with the first reveals that all of the original chapter headings have been retained and some of the original information remains unchanged. Additions to the section on outpatient treatment include first aid and transport, and the last chapter on administrative aspects of burns includes design of a burn unit. Important material on the management of a large number of burns from a disaster is included, based on first-hand experience with the Bradford football-stadium fire of 1985.

Burn shock and fluid resuscitation fills a quarter of this book. Plasma administration is advocated as the cornerstone of initial resuscitation. This practice is no longer common in North America but may be so in the United Kingdom. The estimated volume requirement for the first 24 hours is close to that calculated by the Brooke or Evan's formula, with supplementation orally by water or intravenously by 5% dextrose. The authors do not stress the overall importance of measuring hourly urine output to regulate fluid replacement but attach equal importance to restlessness, colour, blood pressure, nausea and hematocrit value. (They mention crystalloid resuscitation methods and dismiss these as of no greater benefit because hematocrits in patients treated with crystalloid solutions are still high at the end of 24 hours, a state one would expect in the presence of extensive burns.)

Although they recommend the use of plasma, the authors cite the cost and the dangers of transmitting hepatitis and AIDS. They advocate red blood cell administration for burns to 10% or more of the body surface, although earlier they state that patients with burns of up to 15% of the body surface do not even require fluids intravenously. For burns of more than 25% of body surface area, they advocate red blood cell administration 4 to 8 hours and again 24 to 36 hours after injury. Today, unless escharotomies have been performed with excessive blood loss, red blood cells would not normally be administered until after 48 hours.

The book contains a curious mix of detail and lack of detail. For instance, morphine intravenously, 0.2 mg/kg body weight, is advocated but no time interval is given for repeat administration. There are three sentences on how to insert a subclavian line for central venous pressure. Anyone who needs such instruction would require much more detail. Use of Dextrane in the first 24 hours is now of only historical interest but receives a full page, while crystalloid resuscitation, including hypertonic, advocated by Monafo and the Parkland formula of Baxter, both receive only brief mention.

Burns of the respiratory tract occupy two pages including a half-page description on how to do a tracheotomy, compared with three pages devoted to treatment of open wounds. No mention is made of the diagnostic criteria for smoke inhalation, including roles of patient history, bronchoscopic findings, blood gas levels, chest x-ray findings and results of zenon washout, and no treatment principles are included. It is evident that, although smoke inhalation is a major component in comprehensive burn care, these authors regard it as someone else's problem.

The chapter on local treatment of the burn wound is a mix of old and new concepts and includes the only balanced evaluation of different treatment philosophies such as early versus delayed excision. The role of topical antibacterials is touched on and the value of Sulfamylon in penetrating infected wounds is stressed. Today one would probably excise an infected wound. Surprisingly, the important differentiation between bacterial colonization and invasive infection is not addressed, and the value of a full-thickness biopsy for histologic examination and quantitative culture of the wound are missing. The open and closed methods of grafting are discussed, but practical information on the use of sutures, staples, tie-over dressings and splints for grafting across joints is not given.

The usual methods of storage and refrigeration of grafts at 4°C is mentioned. Storage at −4°C, providing 3 months of viable autografts, is advocated. This method has not become common and its inclusion is, I think, misleading. The accepted pretreatment of skin with glycerol and rapid freezing to −70°C is included. For limited donor sites, meshing nine to one is advocated. This technique has not really gained wide practical acceptance and other methods of circumventing limited donor sites are available. The text acknowledges the existence of AIDS and other blood and tissue-transmitted diseases but advocates the archaic and dangerous practice of harvesting extra skin from other burn patients for a patient requiring homograft, without first testing the donor burn patient for AIDS and hepatitis. This practice is to be condemned in 1987.

Escharotomy is buried in a section on management of limb burns but really belongs with initial management. No technical details are included.

The shortcoming of this third edition is its adherence to the original chapter headings and format, which reflect burn problems at the time of initial publication in 1962. Thus, emphasis on plasma for initial fluid resuscitation, sparse mention of the complex problem of smoke inhalation injury and opinions on the role of excisional surgery and topical antibacterial use, which do not reflect present practice, date this book. It would be interesting to know how many of the treatment methods described are actually standard in British hospitals today.

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REOPERATIVE VASCULAR SURGERY. Edited by Hugh H. Trout, III, Joseph M. Giordano and Ralph G. DePalma. 392 pp. Illust. Marcel Dekker, Inc., New York, 1987. $89.00 (US). ISBN 0-8247-7723-9.

This book is one of a series on the science and practice of surgery. Its editors are from The George Washington University Medical School in Washington, DC. The authors are experienced surgeons who present practical solutions to difficult problems.

Vascular surgery has developed rapidly in the past 35 years, so the number of reoperations has also increased. Second operations are more difficult due to scarring and limited options. Few surgeons have extensive experience in this field.

Repeat operations on the vascular system are required by progression of atheroma, myointimal hyperplasia, infection, rejection of transplants or development of false aneurysms. The management of problems such as false aneurysms, infected bifurcation grafts and occlusion of a bifurcation graft are discussed in the book. Less common problems such as failed in-situ vein grafts and reoperations for inferior vena caval obstruction or thoracic outlet compression are also included. There is a chapter on the role of myocardial revascularization for patients with peripheral vascular disease.

The book is attractively printed and has excellent illustrations. It will be valuable for vascular surgeons, for fellows in vascular surgery and any surgeons performing vascular procedures.

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Further Remembrances of That Revered Anatomist, Dr. J.C. Boileau Grant

From access to a detailed curriculum vitae written by Dr. Grant when he was about 75 years old, the author has learned some little-known facts of his background and life.

His ancestors came from France and had been ennobled. One predecessor was a mayor of Paris. Several of his family decided to emigrate to Great Britain with the Huguenot movement.

Grant graduated from the University of Edinburgh in 1908 in the same class as his future brother-in-law, William Boyd.

When World War I was declared, he immediately volunteered for the army. During service on the Western Front, he was mentioned in dispatches in 1916, won the Military Cross in 1917 and a bar to the Military Cross in 1918.

At the outbreak of World War II, Grant, who had been a professor of anatomy first in Winnipeg and then in Toronto for many years, volunteered again for war service, but was rejected as being too valuable a teacher to be allowed to enlist.

Ayant pu consulter un curriculum vitae détaillé écrit par le Dr Grant alors qu'il avait environ 75 ans, l'auteur a appris quelques faits peu connus sur ses antécédents et sa vie.

Ses ancêtres, des gens qui avaient été anoblis, venaient de France. Un d'entre-eux avait été maire de Paris. Plusieurs membres de sa famille avaient décidé d'émigrer en Grande-Bretagne lors du déplacement des Huguenots.

Grant obtint son diplôme en 1908 de l'Université d'Edinbourg. Il était de la même promotion que William Boyd, son futur beau-frère.

A la déclaration de la Première Grande Guerre, il s'est immédiatement porté volontaire a l'Armée. Durant son service sur le front occidental, son nom fut mentionné dans les dépêches militaires en 1916, il remporta la croix militaire en 1917 et ajouta une barrette à sa croix en 1918.

Au déclenchement de la Seconde Guerre Mondiale, Grant, qui avait été professeur d'anatomie a Winnipeg puis à Toronto pendant plusieurs années, se porta de nouveau volontaire. Il fut toutefois rejeté, ses mérites de professeur étant jugés trop importants pour lui permettre de s'enrôler.

Dr. J.C.B. Grant (Fig. 1) died in August 1973 at the age of 87 years. Twelve years before he had written a detailed curriculum vitae, one copy of which was given to his brother-in-law, Dr. David Christie (Grant's wife, Catriona, was a Christie, as was Enid, the wife of Dr. William Boyd). Because I had assisted in caring for him during his final illness and knowing that I had been an anatomy demonstrator for Dr. Grant, Dr. Christie bequeathed the copy to me.

In an early paragraph of the curriculum vitae, written when he was 75 years of age, Grant states:

> My mother was a direct descendant, 20th generation, of Etienne Boileau, who was the first Mayor or Provost of Paris, in the year 1255. Being of the Reformed Church (Huguenots), some of the Boileaus left France for England and Ireland in the year 1685.

According to the Boileau family tree, a John Boileau (fourth generation after Etienne) was ennobled, by King Charles V, and the nobility continued for at least another nine generations, the last of the titled members of the family that remained in France was a Charles Boileau (Dr. Grant's full Christian names were John Charles Boileau).

Grant graduated in medicine from the University of Edinburgh in 1908, in the same class as Dr. William Boyd. During the following year he was for a term resident medical officer at the Infirmary in Whitehaven, Cumberland. From 1909 to 1911, he was a fulltime demonstrator of anatomy in the University of Edinburgh, under Professor Cunningham. He was also a demonstrator of anatomy from 1911 to 1913 at the University of Durham, Newcastle-on-Tyne, under Professor R. Howden, who was the

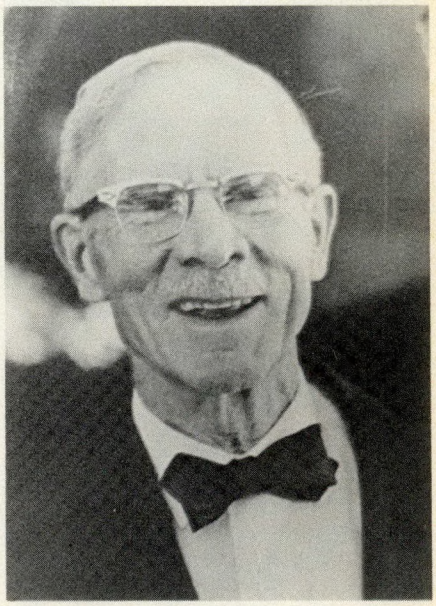

FIG. 1 — Dr. J.C.B. Grant.

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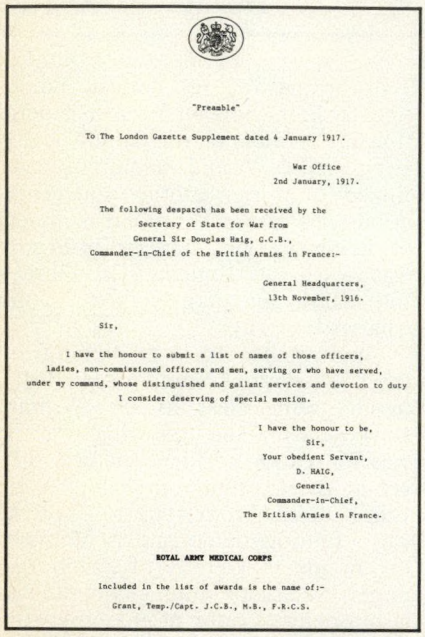
editor of *Gray's Anatomy*. He then served as resident medical officer in the ear, nose and throat department at the Infirmary in Bristol from 1913 to 1914. In the meantime, he was locum tenens numerous times in general practice, to supplement his income.

In his curriculum vitae he titles war service as "Period of the First War":

War was declared by Great Britain on Germany on 4 August, 1914. On the next morning, I wrote to the War Office applying for a commission in the R.A.M.C. and this I did not receive until 2nd November, 1914. I was posted to a regiment of the Rifle Brigade, stationed on the Island of Sheppey. In February 1915, as medical officer I helped to erect the first hospital, 18th general hospital near Le Touquet, Paris Plage. On July 1915, I became medical officer to the 1st Battalion Grenadier Guards. On September 9th, 1917, I asked to be transferred to the 9th Division, for the reason that my remaining brother was adjutant to a Battalion in that Division. I was posted to the 8th Battalion Black Watch (R.H.). On 6th September 1918, I was transferred to 58th C.C.S. to do Ear, Nose, and Throat work. On 17th October 1918, I was transferred to No. 10 Stationary Hospital to continue that work. On 11th November 1918 came the Armistice.



"Preamble"

To The London Gazette Supplement dated 4 January 1917.

War Office
2nd January, 1917.

The following despatch has been received by the Secretary of State for War from General Sir Douglas Haig, G.C.B., Commander-in-Chief of the British Armies in France:-

General Headquarters,
13th November, 1916.

Sir,

I have the honour to submit a list of names of those officers, ladies, non-commissioned officers and men, serving or who have served, under my command, whose distinguished and gallant services and devotion to duty I consider deserving of special mention.

I have the honour to be,
Sir,
Your obedient Servant,
D. HAIG,
General
Commander-in-Chief,
The British Armies in France.

ROYAL ARMY MEDICAL CORPS

Included in the list of awards is the name of:-

Grant, Temp./Capt. J.C.B., M.B., F.R.C.S.

FIG. 2 — Mention in dispatches record.

Military Awards

The curriculum continues:

I was mentioned in Dispatches in September 1916, received a Military Cross (immediate award) in September 1917, and a bar to the Military Cross (immediate award) on August 19, 1918 (2nd army). In April 1919, I was demobilised and returned to Anatomy and Newcastle-on-Tyne.

The exact deed of valour for the mention in dispatches has not been detailed, but was printed in *The London Gazette*, Jan. 4, 1917, and signed by General Sir Douglas Haig, GCB, Commander, the British Armies in France, and dated Nov. 13, 1916 (Fig. 2).

The Military Cross is dated July 31, 1917, place of deed Boisinghe.

T./Capt. John Charles Boileau Grant, M.B., R.A.M.C. For conspicuous gallantry and devotion to duty during attack. Finding that all his stretcher-bearers were occupied, he went forward dressed the cases himself on the spot, sending them back as opportunity arose and stretchers turned up. By this gallant act of devotion he undoubtedly expedited the evacuation of the wounded from the shelled area.

This would have been awarded during the Third Battle of Ypres, during an offensive under General Haig's 5th Army.

The bar to the Military Cross is dated Apr. 19, 1918, place of deed Meteren. This action would have occurred at the start of the last great German offensive, led by General Ludendorf. The offensive continued along the battle lines to the south as far as Chateau Thierry and Rheims for the remainder of the summer and autumn, and then Germany capitulated. It reads:

Bar to the Military Cross
T./Capt. John Charles Boileau Grant, M.C., M.B., R.A.M.C., attd 8th Bn., R. Highrs.

For conspicuous gallantry and devotion to duty. He attended to wounded men lying in the open under heavy fire, and subsequently for three days and nights, with little rest, he was constantly out with stretcher-bearers searching for and removing the wounded. He was undoubtedly the means of saving many lives, and his fine example was of the greatest value at a very trying time.

It has been stated that Dr. Grant, with characteristic modesty about his gallantry, did not collect his medals from Buckingham Palace (Mrs. Grant did it for him later).

When World War II was declared in 1939, Dr. Grant was 53 years of age and had been professor of anatomy at the University of Toronto since 1930. He went to enlist in the armed forces, but because of an inguinal hernia was rejected on medical grounds.

He immediately consulted Dr. Gordon Murray, who successfully operated on the hernia. When he again tried to enlist, he was told his contribution as an anatomy professor was much more important than as a garrison medical officer (Watters N: Personal communication, 1947).

Dr. Grant is remembered as a magnificent teacher (Fig. 3), quick of thought and action. He could draw on the blackboard, using coloured chalks, with either hand or sometimes both hands simultaneously. Lectures were a demonstration of anatomical art, not to be forgotten. At the end of an hour, he would have filled four blackboards with coloured anatomical drawings, more an illustrator than an orator. ■

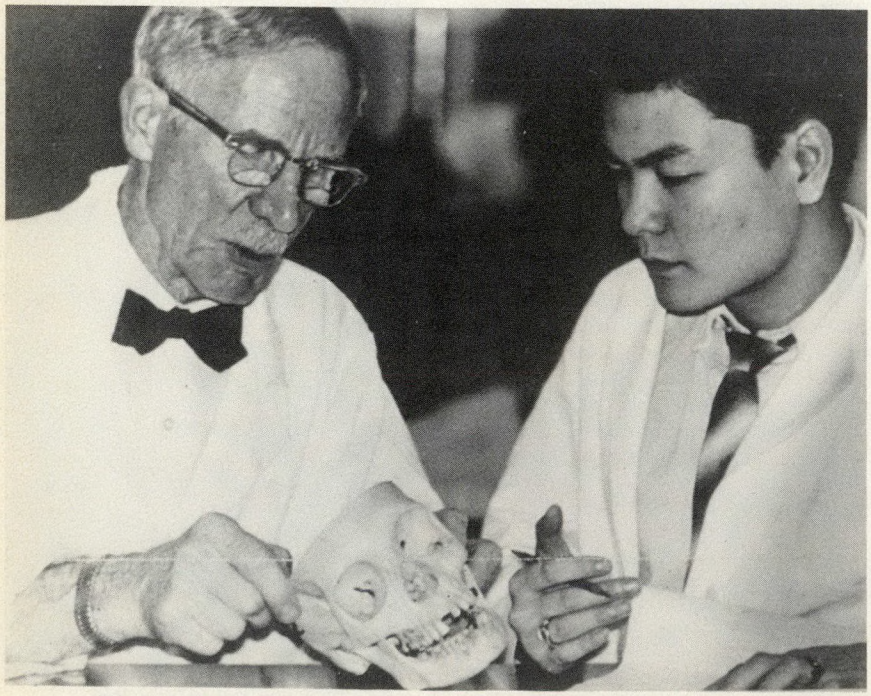


FIG. 3 — Grant demonstrating anatomy of skull to one of his students.

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The Red Deer Regional Hospital Centre has a vacancy for a General Surgeon. An interest in thoracic or vascular surgery is an asset, but not essential.

The Red Deer Regional Hospital Centre is a well-equipped, 400 bed institution, built in 1981, with seven operating rooms plus two others 'shelled in' for future expansion. It serves Red Deer with a civic population of 54,000 and a catchment area of approximately 150,000.

Further information can be obtained by contacting:

Chief of Staff Office
Red Deer Regional Hospital Centre
P.O. Bag 5030
Red Deer, Alberta
T4N 6R2
Phone: (403) 343-4529

S88-16

RD RH

PLASTIC SURGEON: ON – Applications are invited for the position of plastic surgeon at The Victoria Hospital Corporation, London, Ontario. The applicant must be certified in plastic surgery by The Royal College of Physicians and Surgeons of Canada and have a minimum of one and preferably two years of post residency training in some aspect of plastic surgery. The position includes the management of a six bed burn unit. The applicant must express a primary interest in burn care. The position carries an academic rank within the department of surgery at the University of Western Ontario. As such, the applicant must express an interest in ongoing basic research. The appointment is available as of July 1, 1988. Send enquiries to: **Dr. R.M. McFarlane, Department of Surgery, Victoria Hospital, 391 South St., London, ON N6A 4G5.** –S88-20

OSHAWA GENERAL HOSPITAL

PLASTIC RECONSTRUCTIVE AND HAND SURGEONS

The Oshawa General Hospital invites applications for a position in plastic reconstructive and hand surgery on the medical staff for 1988. Canadian fellowship and certificate of specialty competence is required.

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Please contact:

Dr. D.G. Pierson,
Chairman, Department of Surgery
Oshawa General Hospital
24 Alma St.,
Oshawa, ON L1G 2B9 –S88-23

ORTHOPEDIC SURGEON: US – Excellent opportunity to develop orthopedic surgery program affiliated with modern, regional hospital. Excellent guarantee plus full fringe benefits. Beautiful rural area one hour from Canadian metropolitan centre. Enjoy America's most scenic sailing waters. For further information call: **Lianne Harris, President, New England Health Search, 63 Forest Ave., Orono, Maine US 04473. Tel: (207) 866-5680 or 866-5685.** –S88-21

ACADEMIC APPOINTMENT: ON – Applications are invited for a full-time position in the Department of Urology at Queen's University. The successful applicant will have responsibility for teaching in an established postgraduate program involving clinical practice and administration. There are excellent opportunities for basic and clinical research. The applicant must be able to conduct independent research. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. Candidates of either sex are equally encouraged to apply. Please send curriculum vitae and the names of three referees to the attention of: **Mrs. S. Perry, Administrative Assistant, Department of Urology, Queen's University, Kingston, ON K7L 2V6.** –S88-22

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