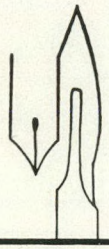
5-1-1985

Volume 28, issue 3

Canadian Medical Association

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.



Percutaneous Transluminal Angioplasty: Under- or Overused?

In 1964, Dotter and Judkins[1] reported a novel approach to the treatment of arteriosclerotic lesions of peripheral arteries. Arterial stenosis or occlusion was dilated percutaneously using a series of coaxial catheters. In 1968, Dotter and colleagues[2] reported their experience with this technique in 155 patients. The success rate was 80% in patients with focal stenosis of the femoropopliteal system but only 29% in patients who had completely occluded segments. In 1969,[3] we reported our experience of percutaneous transluminal dilatation in 15 patients with segmental stenoses of the femoral or popliteal arteries, using Dotter's technique, with early success in 14 patients. In spite of these encouraging results, the procedure did not gain widespread acceptance because of its limited application. It was not until Grüntzig and Hopff[4] developed the double-lumen catheter that the principle of percutaneous transluminal dilatation was accepted. Now the technique is widely used. Although there have been numerous reports on the procedure, its role in the management of patients with peripheral vascular disease has not been clearly defined.

In the March 1985 issue of this Journal (pages 150 to 152), Jones and her colleagues reported on their results of transluminal angioplasty in a high-risk population — those with either rest pain, pregangrene or gangrene. Presumably, such a group, without any intervention, would require amputation in a relatively short time. Of their 85 patients, technical failure occurred in 16. Of the remaining 69, symptomatic improvement was obtained in 40 patients. Nine patients required repeat dilatation from 2 to 51 months after the initial procedure; in five of them, the repeat procedure was unsuccessful. Consequently, of the 85 patients, only 35 (41%) had a successful result for even a short period. The authors' criterion for success, namely avoiding surgery, does not appear to be appropriate, since seven of the patients in whom angioplasty was a technical failure maintained their limbs without surgery. One can only postulate how a similar group of high-risk patients operated on by experienced vascular surgeons, using local or regional anesthesia and both anatomic and extra-anatomic techniques, would have fared.

In our vascular unit we have learned, as have others, that patients with iliac lesions have higher success rates with transluminal dilatation than do patients with femoral or popliteal lesions; that patients who have stenoses have a higher success rate than do patients with complete occlusions; and that the shorter the segment to be dilated and the better the distal runoff, the better is the result.

Since patients who have advanced ischemia generally have multiple levels of disease with poor runoff, in our experience such patients are not generally candidates for transluminal dilatation. In our unit, most patients who have limb-threatening ischemia have been managed surgically rather than by angioplasty. However, in some patients transluminal dilatation of a proximal stenosis has been

The Canadian Journal of Surgery

Le journal canadien de chirurgie

(613) 731-9331

The Canadian Journal of Surgery is published by the Canadian Medical Association and sponsored by the Royal College of Physicians and Surgeons of Canada. The establishment of editorial policy is the responsibility of the Royal College. The objectives of the Journal, endorsed by the Council of the College, are: (1) to contribute to the effective continuing education of Canadian surgical specialists, using innovative techniques when feasible and (2) to provide Canadian surgeons with an effective vehicle for the dissemination of their observations in the area of clinical research.

Published every 2 months by the Canadian Medical Association, PO Box 8650, Ottawa, Ont. K1G 0G8. Printed by Harpell's Press Cooperative, Gardenvale, PQ H0A 1B0. Second-class mail registration No. 5375. Return postage guaranteed. *Subscription rate for Canada and USA $30.00 per year ($15.00 per year for trainees in surgery in Canada only), for all other countries $35.00 per year. Single copies (current issue) available at $5.00 each, back issues at $6.00 each.*

Instructions to Contributors

Detailed instructions to contributors, in English and French, appear on page 95 of the January 1985 issue.

Coeditors
Corédacteurs
L.D. MacLEAN, Montreal, PQ
C.B. MUELLER, Hamilton, Ont.

Associate Editor
Rédactrice associée
G. PANCIROV

The Royal College of Physicians and Surgeons of Canada
Le Collège royal des médecins et chirurgiens du Canada

President / président
J.G. Couture, MD, FRCSC

Executive Director
Directeur général
J.H. Darragh, MD, FRCPC

The Canadian Medical Association
L'Association médicale canadienne

President / président
T.A. McPherson, MD, PhD, FRACP

Secretary General
Secrétaire général
B.E. Freamo

Director of Publications
Directeur des publications
David Woods

Director of Advertising Sales
Directeur de la publicité
P. Griffin (416) 598-9870

Montreal Sales Manager
Chef du service des ventes à Montréal
R. Stapleton (514) 620-8877

Production Manager
Chef du service de la production
K.A. Freamo

combined with distal revascularization. The best results with transluminal dilatation have been in patients with intermittent claudication.

The advantages of transluminal dilatation are that the cost is low and when performed by an expert it is associated with low morbidity and mortality. In the carefully selected patient the results can be excellent. In the patient with advanced disease a more favourable result may be achieved with an appropriately selected operative procedure performed under local or regional anesthesia. There is no doubt that transluminal dilatation is underused in some centres and overused in others. The right place for transluminal dilatation in the spectrum of therapeutic options for vascular disease remains to be determined.

NATHAN M. SHEINER, MD, FRCSC

Member,
Editorial Board.

Surgeon-in-Chief,
The Sir Mortimer B. Davis-
Jewish General Hospital,
3755 Côte Ste-Catherine,
Montreal, PQ
H3T 1E2

References

1. DOTTER CT, JUDKINS MP: Transluminal treatment of arteriosclerotic obstruction; description of a new technic and a preliminary report of its application. *Circulation* 1964; 30: 654–70

2. DOTTER CT, RÖSCH J, JUDKINS M: Transluminal dilatation of atherosclerotic stenosis. *Surg Gynecol Obstet* 1968; 127: 794–804

3. PALAYEW MJ, SEDLEZKY I, SIGMAN HH, SHEINER NM: Occlusive peripheral arteriosclerosis: treatment by percutaneous transluminal recanalization — "The Dotter Procedure". *Can Med Assoc J* 1969; 101: 672–8

4. GRÜNTZIG A, HOPFF H: [Percutaneous recanalization after chronic arterial occlusion with a new dilator-catheter (modification of the Dotter technique) (authors' transl)]. *Dtsch Med Wochenschr* 1974; 99: 2502–5

What Should the Practising Surgeon Do With Precancerous and High-Risk Breast Lesions?

Segmental mastectomy or local tumour resection, with or without postoperative radiotherapy, is becoming increasingly accepted as an approach to stage I and stage II cancers of the breast. The contributors to the symposium on precancerous and high-risk breast lesions, which appears in this issue of the Journal (pages 242 to 267), recommend a more aggressive approach to these lesions than that practised by many surgeons today. Therefore, I must ask myself whether I am comfortable carrying out total breast removal, either conventionally or subcutaneously, in order to avoid cancer. Moreover, I must question whether any of these precancerous entities, which are so repeatedly referred to in the literature, have ever been proven to develop into invasive cancer.

Certainly there are high-risk lesions and high-risk patients. The risks relate to the epidemiologic, historical and clinical characteristics and to the microscopic interpretation of biopsied material. These factors must be considered when the decision is made, first, whether to biopsy and, second, whether to repeat the biopsy, follow up conservatively or recommend further surgery.

At one extreme is the case of an obese woman who has never experienced a full-term pregnancy; she has a 40-year-old sister with breast cancer and now, because a precancerous breast condition is diagnosed, total mastectomy is recommended. Whether the same recommendation would be made if the only clinical high-risk factor was diffuse mammographic change is questionable and would seldom be a determining factor in my judgement.

The confusion is further promoted by what I like to call the pathologic indecisiveness of the multiple diagnoses offered on biopsy material. Seven different categories of breast lesions are noted by the symposium panelists. What is the clinician to understand when he hears the words carcinoma in situ, intraductal carcinoma, noninvasive ductal carcinoma, diffuse atypical hyperplasia, papillomatosis, adenomatosis, sclerosing adenosis, lobular dysplasia, lobular carcinoma in situ or diffuse cystic hyperplasia with atypism? These confusing interpretations of biopsy specimens may not mean the same to pathologists and to clinicians.

I do not recommend, in the understanding, intelligent patient who can be followed up regularly, that, based upon the above diagnoses alone, she have prophylactic removal of her breast. However, some recommendation for management must be made. The patient must understand that there is no cookbook answer to this dilemma and if she is not willing to assist us in finding the answer by being followed up conservatively, then she should be encouraged to undergo definitive surgery. While controversy exists as to what is, or is not, a precancerous condition of the breast, the patient must be aware of this dilemma and assume some of the decision-making responsibility for her management.

Subcutaneous mastectomy should not be used to treat infiltrating breast cancer. Selectively, it may have a role in the management of severely atypical lesions as determined by clinical, mammographic or microscopic interpretation. Unfortunately, the usual subcutaneous mastectomy leaves a "padded" layer of subcutaneous tissue beneath the skin, particularly beneath the nipple, which contains isolated glandular and ductal elements of the breast. Whether 5%, 10% or 15% is left after subcutaneous mastectomy, there still remains a risk of cancer, for that portion of remaining breast is at the same risk as was the entire breast. The more breast tissue removed, the less likely the patient is to get cancer, but also the less likely one is to achieve a satisfactory cosmetic result. With the placement of the implants beneath the pectoralis muscle, the plastic surgeon can often do what he calls a total mastectomy, leaving only a small amount of glandular tissue beneath the nipple-areolar complex, but breast tissue is left unless, possibly, the nipple is transplanted. Under those circumstances, in order for the transplanted nipple to remain viable, essentially a full-thickness or sometimes a split-thickness graft remains after débridement of all the tissue beneath the areola and the nipple. It has been my experience, however, that few patients are satisfied with the cosmetic results of subcutaneous mastectomy or immediate implant after what I call a 99% breast removal, leaving skin and nipple intact. I recommend that if removal

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

of breast tissue is indicated because of cancer or the high risk of cancer, then the breast tissue should be removed in its entirety and reconstruction undertaken immediately, or after a suitable interval. I find that cosmetic success is achieved more readily if the reconstruction is undertaken 6 to 10 weeks after breast removal. There are, of course, exceptions. When the patient and her husband express strong interests in preserving the original breast, skin, nipple and contour, we will agree to subcutaneous mastectomy with multiple biopsies being carefully analysed, especially in those cases in which the breast is diffusely nodular, virginally firm or difficult to evaluate.

When such prophylaxis is decided upon, there is the controversy over how the opposite breast should be handled. Both glands have the same embryologic origin and should therefore carry the same risk of tumour development. The opposite breast is not considered for surgery unless it is biopsied for diagnostic reasons based upon the pathological findings in the affected breast. If total mastectomy is decided upon for the premalignant lesion, then the opposite breast should presumably be left intact except for biopsy. Further intervention would be indicated by the biopsy findings. Cosmetic symmetry is difficult to obtain and as long as the contralateral breast remains clinically normal or minimally abnormal, it should be preserved.

Only with time, careful patient monitoring by cooperative group studies and appropriate interpretation and follow-up of the many pathologic entities will we know what to do with the breast containing "precancerous" lesions. The intelligent, cooperative, understanding patient should be offered conservative treatment with regular follow-up and repeat biopsies at regular intervals. The biopsy can be done by needle, trocar or open technique. Semiannual low-dose mammography might be helpful. It is essential that these patients become meticulous self-breast examiners and with the help of their husbands carry out a conscientious weekly breast examination. I recognize that cancer of the breast remains one of the more frequent causes of death in women. In spite of this, it is difficult to recommend aggressive surgery for a disease that has yet to be proven to be truly a precursor of cancer.

ALFRED S. KETCHAM, MD

Chief, Division of Oncology,
Professor of Surgery and Oncology,
American Cancer Society Professor of Clinical Oncology,
Department of Surgery,
University of Miami School of Medicine,
PO Box 016310,
Miami, Fla. 33101
USA

For prescribing information see page 271

The restoration of a work of art requires the right tools in the hands of a master

NEW

*SURGICEL NU-KNIT**

Absorbable hemostat
(oxidized regenerated cellulose)

Stronger, high density format. One ply effectively handles problem bleeding and can be easily removed or sutured if required.

Unique bactericidal activity *Only oxidized regenerated cellulose provides bactericidal protection against postoperative growth of pathogens and wound infection in vivo.*[1] *Absorbable gelatin sponge, topical thrombin and microfibrillar collagen have been shown to actually enhance bacterial growth.*[2,3,4]

Rapid absorption *Both SURGICEL NU-KNIT* and SURGICEL* are rapidly absorbed in 7 to 14 days, with virtually no tissue irritation as demonstrated in vivo.*[1]

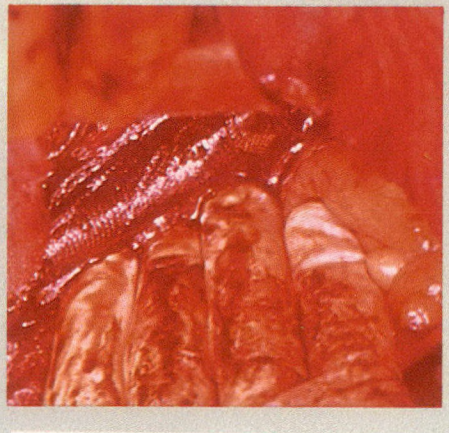
*& SURGICEL**

Absorbable hemostat
(oxidized regenerated cellulose)

Versatile, low density knitted fabric. Multiple folds can be packed in hard-to-reach places and removed easily when hemostasis is achieved.

Rapid, dependable hemostasis *Positive bleeding control is usually achieved in clinical situations in one to two minutes without the addition of other agents. Under severe test conditions, bleeding is usually controlled within five minutes by SURGICEL NU-KNIT* and within eight by SURGICEL*.*[5]

Easy to handle *Oxidized regenerated cellulose conforms readily to irregular surfaces; won't unravel or fray when cut; won't stick to wet gloves or instruments.*



hémostatique résorbable
(cellulose régénérée oxydée)
SURGICEL NU-KNIT*
absorbable hemostat
(oxidized regenerated cellulose)

hémostatique résorbable
(cellulose régénérée oxydée)
SURGICEL*
absorbable hemostat
(oxidized regenerated cellulose)

Johnson & Johnson

When technique is an art

Available in convenient sizes.

1. Dineen P: Infections in Surgery, 2:441, June 1983.
2. Dineen P: Surg, Gyn & Ob 142:481, April 1976.
3. Hill G: Infection and Immunity 19:443, 1978.
4. Dineen P: J Surg Res 23:114, 1977.
5. Data on file, Johnson & Johnson Research.

CORRESPONDENCE

Contributions to the Correspondence section are welcomed.

They should be typewritten and double spaced.

Human Bite Injuries of the Hand

To the editors.—My experience with human bite injuries of the hand at the Ottawa Civic Hospital over the past few years prompts me to respond to Dr. Bite's article (*Can J Surg* 1984; 27: 616–8).

Through this experience we have adopted a policy whereby all these injuries are referred to the plastic surgery service, whether the patient presents early or late after injury. All bites that have penetrated the full thickness of the dermis are extended and explored under local anesthesia to determine, as early as possible, whether or not the integrity of the underlying joint or tendon has been violated. Leaving the wound open and prescribing antibiotics orally is simply not adequate treatment in our experience. All patients with open joints who present with cellulitis or suppuration should, in our view, be admitted to hospital for parenteral administration of antibiotics. It is essential that the integrity of underlying joint and tendon be established as early as possible and this can only be done by exploring and visualizing the structures. Dr. Bite makes no mention of this as a policy although he does allude to the need for copious irrigation of wounds. Treating patients with active infection expectantly as outpatients and giving antibiotics orally has almost always resulted in advanced complicated infections with severe morbidity and permanent disability of the involved hand. To rely on clinical evidence of septic arthritis will inevitably give a false sense of security to the surgeons dealing with these injuries. The time to establish joint integrity is as soon after injury as possible and before active septic arthritis supervenes.

I would, therefore, make a plea to all surgeons involved in the management of human bites to adopt this more aggressive approach in the interests of superior results, lower morbidity and disability, and, in the long run, a saving of health-care resources.

G. ALLAN TAYLOR, MD, FRCSC

Chief, Division of Plastic Surgery,
Ottawa Civic Hospital,
Ottawa, Ont.
K1Y 4E9

To the editors.—Dr. Taylor raises some important points about the management of human bite injuries of the hand. I certainly agree with him that the wound should be examined under local anesthesia at the time of initial assessment when irrigating it. If penetration of the joint capsule or tendon sheath is discovered, more aggressive management with parenterally administered antibiotics, hospital admission and possibly formal operative exploration is warranted. However, in the absence of such findings, when the clinical findings are minimal and the patient is seen within 24 hours of injury, I disagree with Dr. Taylor. Statistical analysis of my results showed no significant difference in outcome (as measured by duration of hospitalization, duration of outpatient follow-up required and complication rate) between patients seen within 24 hours of injury, those assessed from 1 to 7 days following injury and those initially seen more than 7 days following injury. Furthermore, Malinowski and colleagues[1] prospectively studied 265 patients with human bite injuries of the hand and concluded that there was no difference in outcome and complication rates between 131 hospitalized patients treated parenterally with antibiotics and 134 similar patients treated as outpatients and given antibiotics orally. All had minimal clinical findings at the time of initial assessment and, in fact, the highest complication rate (4.7%) occurred in the hospitalized group. Thus, if all patients with human bite injuries were admitted to hospital, at least 50% would be admitted unnecessarily. I stress that I only recommend outpatient management for those patients with minimal clinical findings (no septic arthritis, no purulent drainage and no cellulitis) who are seen within 24 hours of injury. If such a course of management is adopted, the patient should be re-examined within 24 hours, preferably by the same physician. To admit all such patients to hospital is unjustified and an unnecessary expense on the basis of the available data.

ULDIS BITE, MD, FRCSC

Apt. C20,
2015 - 41st Street NW,
Rochester, MN 55901
USA

Reference

1. MALINOWSKI RW, STRATE RG, PERRY JF JR, FISCHER RP: The management of human bite injuries of the hand. *J Trauma* 1979; 19: 655–9

Head Injuries

To the editors.—I read with great interest the excellent article "Head injuries: a prospective, computerized study", by Parkinson, Stephenson and Phillips (*Can J Surg* 1985; 28: 79–83). The article is full of valuable information that will make it widely read and cited. Nevertheless, the authors make two controversial statements that can likely be buttressed by information collected in their study but which are made without reference to supporting data.

The first deals with the effect of "intensive" therapy that includes "intracranial pressure monitoring, paralysis, ventilation and barbiturates". When compared with that of patients treated by simply "maintaining an airway and giving mannitol, based on clinical indications..., patients treated more intensively... did less well as a group than might have been expected", the authors claim. One may surmise that among the 323 patients

– For prescribing information, see page 290

reported to have had cerebral contusion or intracranial hematomas, or both, there might have been approximately 100 patients who had raised intracranial pressure, as intracranial hypertension may be expected to develop in roughly one third of patients with severe head injuries.[1] One hundred patients carefully studied would suffice to support or refute the contention that "intensive" therapy is not effective. I should like to know how many patients were monitored, whether the patients who died did so because of intractable intracranial hypertension, whether the intensive and the nonintensive groups were comparable with respect to coma scale, associated injuries, and so on. It is well known that random assignment, even when formally done, may produce groups with significant differences in important features that make comparisons more difficult.

The second concept that I consider controversial is the implication that with "no history of a lucid interval" patients "were unlikely to have been saved had they arrived in hospital earlier". Dr. Parkinson and his colleagues do not cite the article by Seelig and associates[2] who presented data suggesting that early treatment of acute subdural hematomas was more likely to produce a favourable outcome. At the very least, I should like to know how many patients died before arrival at the Health Sciences Centre in Winnipeg and, of those, how many were hospitalized at smaller hospitals before they were transferred.

MICHAEL SCHWARTZ, MD, M SC, FRCSC

Department of Neurosurgery,
Sunnybrook Medical Centre,
2075 Bayview Ave.,
Toronto, Ont.
M4N 3M5

References

1. SCHWARTZ ML, TATOR CH, ROWED DW, REID SR, MEGURO K, ANDREWS DF: The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. *Can J Neurol Sci* 1984; 11: 434–40

2. SEELIG JM, BECKER DP, MILLER JD, GREENBERG RP, WARD JD, CHOI SC: Traumatic acute subdural hematoma. Major mortality reduction in comatose patients treated within four hours. *N Engl J Med* 1981; 304: 1511–8

SESAP IV Question

118. Patients with major injury of the liver associated with hemorrhage

(A) frequently require hepatic lobectomy

(B) require T-tube drainage of the biliary tract

(C) can usually be managed by local hemostasis and débridement

(D) rarely die with current management techniques

(E) often require ligation of the hepatic artery for control of bleeding

For the incomplete statement above select the one answer that is best of the five given. For the critique of Item 118 see page 223.

(Reproduced by permission from *SESAP IV Syllabus; Surgical Education and Self-Assessment Program No. 4.* For enrolment in the Surgical Education and Self-Assessment Program No. 4, please apply to the American College of Surgeons, 55 East Erie St., Chicago, IL 60611.)

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.

Portrait of the Canadian Surgeon: Not a Young Man

Compared with other specialists in Canada, surgeons and their colleagues in anesthesia are an aging group — of men — according to statistics emerging from the Canadian Medical Association's data bank on practising physicians.

The figures show that almost 60% of surgeons are older than 45 years and, in the next 10 years, almost 30% will be 65 years of age or older. In fact, in the next 5 years, 20% will have reached or surpassed the age of retirement. The category "surgery" encompasses cardiovascular, thoracic, orthopedic, plastic and vascular surgery as well as urology and neurosurgery.

The statistics are part of an extensive report coauthored by Orvill Adams, CMA's Director of Economics, and scheduled to appear in the *Canadian Medical Association Journal* this month. The report marks the first release of information compiled from 41 599 replies to a questionnaire sent out by the CMA in 1982 to all physicians residing in Canada; 87.4% of them responded, indicating that the figures accurately reflect the medical profession in Canada.

According to the data, just over 9% of Canada's physicians are surgeons; 85% work full-time and almost all the rest are semiretired. Although women account for about 14% of all physicians, they represent only 1.8% of surgeons, possibly as much a reflection of the age distribution of surgeons as any other reason, since women have only recently entered the medical profession in large numbers.

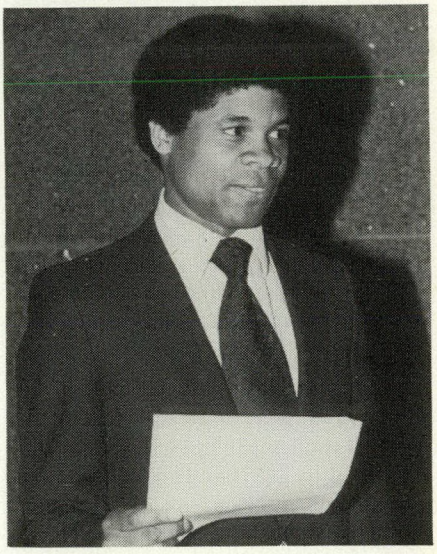
The data leave no question about who is practising surgery in Canada; the implications of what they portray are less clear. Whether the rate of attrition currently being experienced will put surgical services at a premium is particularly nebulous because the data do not show how much time surgeons now spend in primary practice. What they do show is how much time general practitioners spend performing surgical interventions. Of the 12 276 general practitioners who stated that the word "general" best described their practices, 46.3% spend at least 4 hours each week in the operating room. Of the 2411 who noted that their practice was not general, 3.1% categorized their work as general surgery.

Shortage of Surgeons Offset by Oversupply of GPs

The Federal/Provincial Advisory Committee on Health Manpower has forecast a shortage of surgeons by the year 2000 but apparently expects general practitioners and other medical specialists to meet the demand for services. Not yet formally released, that committee's findings were circulated internally in a preliminary report last fall and recently attracted media attention because it predicted an 18% surplus of general practitioners and medical specialists.

The committee recognized the inadequacy of its data but believed they were sufficient to indicate overall trends towards an oversupply. Allowing for shortages in surgical and laboratory specialties, the committee forecasts a total surplus of 12%. The methods the committee used to calculate future requirements for physicians have been criticized, since they were based primarily on physician-to-population ratios and past supplies.

"The ratio is so crude... I prefer not to use it," commented Adams who went on to explain that his department shies away from the use of physician-to-population ratios mainly because they have become the sole measure and "they don't really show what you need to know. You need to know what resources you have in an area and the population you are trying to serve. But you also need to know what type of health system you are working toward." The big question is: What does one compare the figures to? Comparing them to those of the past assumes that the system was perfect previously, and comparing them to those in other countries is probably even less useful. Said Adams, "It's ridiculous to compare physician-to-population ratios in Canada with those in the US. The countries deliver health care in a different way."



Adams: "physician-to-population ratios crude".

Nevertheless, based on its figures, the committee recommended measures to avert the future oversupply of physicians by curbing increments from every source. It called for cutbacks in annual immigration of physicians recruited to fill positions for which no Canadian can be found, in licences being given to foreign-trained graduates (including Canadian citizens), in postgraduate training in medicine and in medical school enrolment. The committee also recommended that postgraduate training be rationalized

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

to fill the ranks of specialties in which shortages are perceived.

If implemented, the across-board reductions will likely affect some provinces more than others. In the past, Saskatchewan and Newfoundland have been particularly dependent on immigrant physicians. For example, according to Adams's figures, more than half of surgeons in the age group 55 to 65 years who are practising in Saskatchewan received their education outside Canada, and the percentage for all surgeons in Saskatchewan is 46%. The latter compares with 26% for surgeons country-wide and 28% for all physicians. As might be expected, the United Kingdom was the source of almost half the surgeons aged 55 to 65 years and, together with India, accounted for nearly half of all surgeons trained outside Canada.

These figures suggest that, in the not-too-distant future, surgeons will be scarce in some areas of the country. Trends in the popularity of different fields of medicine may be partly responsible for the current picture, although the number of surgical residents trained annually has not changed much over the past 10 years. According to data from the Royal College of Physicians and Surgeons of Canada, an average 190 residents have gained certification yearly for the past decade in the specialties constituting the surgical category referred to by the federal/provincial committee.

Overall, fluctuations have been offset from year to year, but the tendency has been away from general surgery towards greater specialization. In 1975, 94 general surgeons gained certification, whereas the figure for 1984 was 60, reflecting a relatively steady decline over the years. In other words, the supply of surgeons is likely dwindling, and the ones being trained differ in focus and skills from those trained in the past.

Couture: "Strengthen Broad-Based Specialties"

It is this change in the shape of specialization that was the focus of discussions in mid-March when the medical specialties' boards of the United States and Canada met in Chicago.

Speaking to the group during a plenary session of the day-long meeting, Royal College President Jean G. Couture said that the move towards increasing subspecialization was taxing the resources of the medical schools and undermining the schools' mission to produce well-rounded physicians.

He noted that the number of operating procedures done by general surgeons has decreased and he called for a strengthening of the broad-based specialties. Couture, who is head of surgery at Laval University, said the approach to patients is "microscopic and fractionated", and the effects on teaching and research have probably been compounded by the efforts of medical faculties to seek out renowned experts in particular fields. The result is an absence of generalists as role models and an increase in the costs of care.

The high costs of subspecialization came up again and again at the meeting, with speakers focusing on the large sums of money involved even in the development of an examination for certification in a new specialty. The questionable cost-effectiveness of a pulmonologist's doing general medicine 85% of the time was raised as an example.

The consensus seemed to be that subspecialization is inevitable as a response to scientific advances in knowledge and equipment, but that public needs should be a major criterion in the creation of a subspecialty.

No one argued that specialization was not just a response but often a source of technical and scientific advances. University staff with narrowly specialized skills often attract funds for research and development.

Two University-Affiliated Centres Get Funds for Research and Development

Both University Hospital, London, Ont., and Sunnybrook Medical Centre, Toronto, have recently announced investments from nongovernment groups to develop sophisticated techniques and equipment. Scientists at University Hospital will be collaborating with Biomedical Instrumentation Inc. to produce a cardiac mapping device that will simplify surgical management of patients with heart rhythm disorders. The computer-assisted device will be used in the operating room to identify the location of malfunctions causing cardiac arrhythmias.

In Toronto, Sunnybrook Medical Centre has obtained funds from a major European foundation to develop a biomechanical laboratory in which biomaterials for bone surgery, joint replacement and fracture fixation will receive special attention. Joseph Schatzker, MD, FRCSC, who has recently been appointed head of orthopedic surgery at the centre, will direct the work, drawing on his expertise in joint reconstruction and musculoskeletal trauma.

Schatzker replaces Marvin Tile, MD, FRCSC, who has been promoted to deputy head of surgery at Sunnybrook Medical Centre.

Other Appointments and Honours

S.J. Peerless recently became the first appointee to the C.G. Drake Professorship in Neurosurgery at the University of Western Ontario; the position is for 5 years and was established to honour Drake for his achievements in brain surgery.

Clement McCulloch, MD, FRCSC, was the 1985 recipient of the medical achievement award, given out annually since 1979 by the Canadian Association of manufacturers of Medical Devices. The award, presented at the association's annual general meeting on Apr. 15, 1985, was recognition for McCulloch's work in ophthalmological research.

AMY CHOUINARD

Drs. Drake (left) and Peerless honoured at Western.

REVIEW ARTICLE

J.P. McELWAIN, MB, FRCS(I);* G.A. HUNTER, MB, FRCS, FRCSC;† E. ENGLISH, MD, FRCSC‡

Syme's Amputation in Adults: a Long-Term Review

A retrospective study was undertaken in two patient populations to establish the failure rate of Syme's amputation. Failure was defined as an amputation requiring revision to a more proximal level. For traumatic lesions of the foot the failure rate was 29% and for dysvascular lesions it was 41%.

The long-term functional results in 55 patients who underwent Syme's amputation for traumatic, dysvascular or congenital lesions were studied. Overall, 73% had good function. The ideal Syme's stump, where the fat pad is centred securely over the distal tibia, was noted in only 22% of patients. The authors conclude that, in the past, technical details may have been overemphasized, because in this study the functional results of Syme's amputation were more dependent on prosthetic fitting. This type of amputation is not recommended for patients with dysvascular lesions because of the high failure rate.

Une étude rétrospective a été faite au sein de deux populations de patients dans le but d'établir le taux d'échec de la technique d'amputation de Syme. L'échec a été défini d'après la nécessité de procéder à une révision à un niveau plus proximal. Le pourcentage d'échec fut de 29% dans les cas de lésions traumatiques du pied et de 41% pour les problèmes d'origine vasculaire.

On a étudié les résultats fonctionnels à long terme de 55 amputations de Syme pour lésions traumatiques, dysvasculaires ou congénitales. Dans l'ensemble, de bons résultats ont été obtenus dans 73% des cas. Le moignon idéal dans la technique de Syme est obtenu quand le tissu adipeux est bien centré autour de la partie distale du tibia; un moignon idéal n'a été observé que chez 22% des patients. Les auteurs concluent que, dans le passé, les détails techniques de l'opération ont possiblement été exagérés puisque, dans cette étude, les résultats fonctionnels de l'amputation de Syme ont été davantage reliés à l'ajustement de la prothèse. Ce type d'amputation n'est pas indiqué pour les patients souffrant de lésions dysvasculaires, vu le haut taux d'échec.

From the Division of Orthopedic Surgery, Sunnybrook Medical Centre, Toronto, Ont.

**Clinical Fellow in Orthopedic Surgery, Sunnybrook Medical Centre*

†Associate Professor of Orthopedic Surgery, University of Toronto

‡Consultant Orthopedic Surgeon, Scarborough General Hospital, Scarborough, Ont.

Accepted for publication Jan. 2, 1985

Reprint requests to: Dr. G.A. Hunter, Division of Orthopedic Surgery, Sunnybrook Medical Centre, 2075 Bayview Ave., Toronto, Ont. M4N 3M5

The continuing role of Syme's amputation in treating traumatic injuries to the foot, peripheral vascular disease, diabetes mellitus, and congenital and neurologic problems is still debated in the literature. Despite its advantages, it has not gained total acceptance or popularity since it was first introduced by Syme[1] in 1843. Many[2-5] have found that long-term function is satisfactory in most amputees, except those in whom the amputation is performed for peripheral vascular disease and diabetes mellitus. In these circumstances the high revision rate is unacceptable.[6]

The success of Syme's amputation in children is well documented.[7-9] It has unique end-bearing characteristics, it permits continued growth of the tibia so that the patient may walk with or without a prosthesis and the stump has proved durable, enabling the patient to lead a normal life.

Because of the study of Harris,[10] Syme's amputation has enjoyed considerable popularity in North America. Reviewing the history of the amputation and the various modifications, he outlined the importance of attention to technical detail, which includes disarticulation through the ankle, preserving the blood supply to the flap, transecting the tibia parallel to the floor and not perpendicular to the tibial shaft, avoiding buttonholing the skin and preventing migration of the fat pad in the early postoperative period. Emphasis on surgical technique has been reported by others,[11,12] confirming that the success of this procedure depends on meticulous attention to technical detail.

Over the years, dissatisfaction and the revision rate have increased among patients with traumatic amputations attending the Workers' Compensation Board Rehabilitation Centre of Ontario. In this retrospective review, patients who underwent Syme's amputation for traumatic and nontraumatic lesions were studied to establish the overall revision rate and to evaluate long-term function.

Patients

The medical records of 132 patients attending The Workers' Compensation Board Rehabilitation Centre in Toronto and 56 patients attending Sunnybrook Medical Centre who underwent Syme's amputation were reviewed. The factors considered were the number of surgical procedures performed before the definitive Syme's amputation, the number of amputations revised to a more proximal level, the time of revision (early or late) and the reason for revision. If the revision was undertaken within 3 months of amputation it was considered early, thereafter it was regarded as late.

A total of 54 patients with 55 amputations were personally reviewed (J.McE.). These form the basis for much of this report. Four were women, the remainder were men. Of the 55 amputations, 35 were for injury, 6 for congenital or neurologic lesions and the remaining 14 were for peripheral vascular disease and diabetes mellitus. The average follow-up was 29 years (range from 1.5 to 65 years) for the patients with trauma, 6.5 years (1.5 to 10 years) for the dysvascular patients and 31 years for those with congenital and neurologic lesions. The average age at follow-up was 56 years, patients with dysvascular limbs being on average 8 years older.

One patient had a bilateral Syme's amputation. Eleven had contralateral

amputations (7 below-knee, 1 Gritti–Stokes, 1 ray resection, 1 transmetatarsal amputation and 1 toe resection). All patients were assessed with regard to pain, use of a prosthesis, size, shape, position and mobility of the stump, employment and overall function, including recreational activities. The need for further surgical procedures was also recorded. We used a modification of the Hornby and Harris[13] functional rating system. For a good result, the patient had to be fully employed at his original occupation or a similar one, wearing a prosthesis full-time with no restriction of social activities. Minor stump pain, not necessitating regular prosthetic adjustments, was tolerated in this group. Change of occupation to a more sedentary job, pain necessitating regular prosthetic changes and restriction of social and recreational activities were considered a fair result only. Poor results were those in which the patient complained of persistent pain and discomfort, did not wear the prosthesis full time and was unemployed or retired prematurely as a direct result of the amputation. Modifications in this rating system were made for patients who had retired because of old age.

The shape of the stump was described as either conical, round, bulbous or flat. The mobility of the stump was classified using the criteria outlined by Murdoch,[5] as follows: grade 1 — the heel pad was securely fixed to the tibia; grade 2 — the substance of the pad could be moved from side to side without uncovering the peripheral bone; grade 3 — the heel pad could be displaced in all directions, leaving part of the peripheral bone unprotected; grade 4 — the heel pad was grossly mobile and permanently displaced (Figs. 1 to 4). Bone irregularities of the lower tibia were assessed by standard anteroposterior and lateral roentgenograms.

Results (Table I)

Trauma Group

Twenty-two of the 35 patients complained of pain in the stump, but it was severe in only 10. Eighty-two percent of the amputees returned to their original jobs, 31% of them doing heavy labouring work such as underground mining. Walking supports were used by eight patients because of old age. Patients with contralateral amputations tended to use supports when walking long distances; 20 patients could walk an unlimited distance. Only 17% of patients considered that they were end weight bearing on the stump while wearing the prosthesis; the remainder bore more weight proximally.

Further minor surgical procedures were necessary in 17% of the patients in this group. Technically, 22% of patients had good stumps and 3% had poor stumps. The remaining stumps, although functional in most cases, tended to migrate, predominantly to the medial side of the tibia. The major long-term complication, as related by the patient, was migration of the fat pad.

Dysvascular Group

All but 1 of the 14 patients in this group wore a prosthesis full time. This includes four patients with contralateral amputations requiring prostheses. Only two patients could weight bear at the end of the stump. All but three patients had retired, either because of old age or generalized systemic disease.

Three patients could walk an unlimited distance while the remainder were restricted by intermittent claudication. Twelve of the 14 patients thought they bore more weight at the knee.

Congenital Group

Three patients suffered stump pain, but it did not compromise their activity. All six in this group had worked at some stage, although two have now retired.

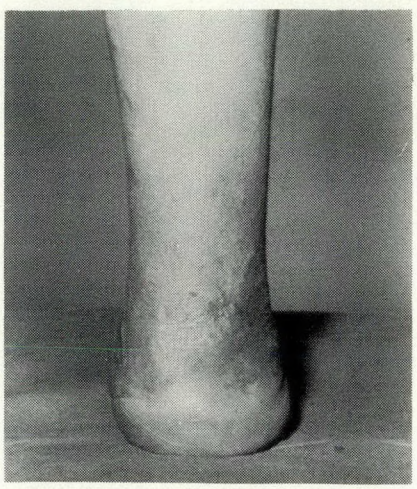


FIG. 1—Grade 1 mobility. Heel pad is securely fixed to tibia.

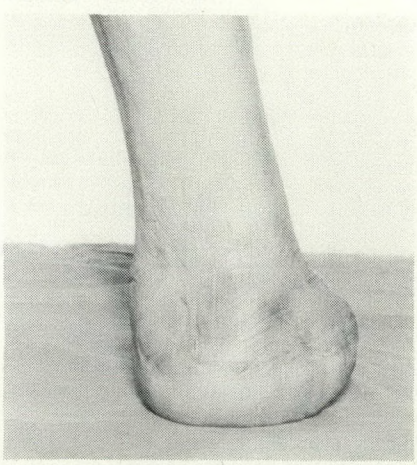


FIG. 2—Grade 2 mobility. Substance of heel pad can be moved anteriorly without uncovering peripheral bone.

End weight bearing on the stump without the prosthesis was possible in four patients but not by the two who have retired. None of the patients had an ideal Syme's stump, but all were functional. Every patient was satisfied with the end result. No further surgical procedures were performed in this group.

Failure Rate

This was defined as the number of Syme's amputations requiring a revision to a more proximal level. Of 132 traumatic amputees, 38 (29%) amputations were revised either to a standard below-knee or a long below-knee amputation. Approximately 60% of the revisions were performed for stump pain, the remainder for prosthetic problems and stump infection. The interval between the initial amputation and revision ranged from 2 months to 61 years. In this group of failures, the average number of operative procedures before the elective Syme's

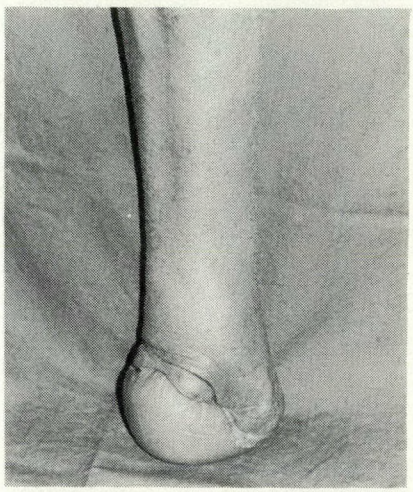


FIG. 3—Grade 3 mobility. Heel pad is displaced laterally, leaving medial side unprotected.

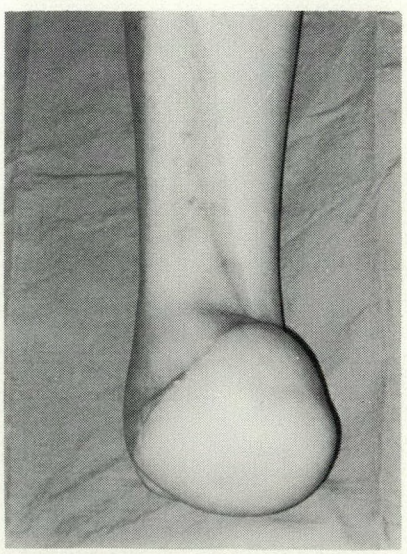


FIG. 4—Grade 4 mobility. Heel pad is permanently displaced anteromedially.

operation was 5 (ranging from 2 to 14) compared with an average of 3.3 procedures for the whole group of trauma-related amputations.

Of the 56 amputations for dysvascular lesions, 23 (41%) were converted to a higher level (20 below the knee, 2 above the knee and 1 through the knee). All but three were performed within 3 months of the original procedure for infection and wound breakdown. Of patients in this group, 22 (40%) died within 6 months of the revision; 12 of them had a two-stage procedure carried out before failure occurred.

Discussion

The failure rate of Syme's amputation in this series for both traumatic and dysvascular lesions was high. Many of the failures have been ascribed to poor surgical technique and patient selection.[2,10,12] It is understandable that infection in the dysvascular limb predisposes to failure, and the clinical diagnosis of tissue viability in this group is not reliable. Because this study is retrospective, we cannot comment on the condition of the stump at the time of revision. We do know from the clinical results that a technically inferior Syme's stump is compatible with good function when the prosthesis is modified. Because pain was the major reason for revision in the traumatic group, and because each patient had had an average of five operations before their elective Syme's amputation, it is possible that these patients fit into a special chronic pain category, for example, mania operativa.[14] If one could identify these difficult patients, it may be prudent to proceed with an early elective amputation in preference to multiple procedures to preserve a severely injured foot.

Good clinical results were recorded in 73% of the entire series of patients. Pain was a predominant reason for poor function. If modifications in the prosthesis had not been made, it is possible that an even greater number of patients would have been in this category because of the condition of their stumps.

The ideal Syme's amputation according to the literature consists of securely fixing the fat pad to the broadest area of the cut end of the tibia — the cut end being parallel to the floor and not perpendicular to the tibial shaft. Centrally positioned fat pads on weight bearing were recorded in only 22% of amputations in the entire series; all gave good function. Medial, lateral and posterior migration of the fat pad predominated in the remainder but did not preclude a good functional result. End weight bearing, with or without the prosthesis, was possible only in a minority of these patients, suggesting that good prosthetic fitting was probably the reason why these amputees functioned so well.

Modern Syme's amputation involves disarticulation of the ankle joint combined with excision of both malleoli, as a one- or two-stage procedure.[15] The articular cartilage is not removed and consequently because of the shape of the distal tibia its surface is not parallel to the ground in both the anteroposterior and transverse planes. How securely the fat pad can be centred over the cartilaginous distal tibia is questionable. It appears to us that both these modifications account for the frequent migration of the fat pad.

In the presence of infection, two-stage amputations have been advised.[15,16] Of the 17 such procedures performed for infection in dysvascular limbs in this series, only 5 were successful. This success rate was considerably lower than in other reported series. It has been our policy in the past to try and preserve as much of the foot as possible, and the elected site of amputation was based on clinical grounds only. We are now using the Doppler ischemic index[15] in an effort to evaluate the most suitable level for amputation, and select suitable patients for ankle disarticulation.

Undoubtedly, the best results for Syme's amputation were for the congenital lesions. These patients are younger, well motivated and adapt to the prosthesis quickly. They do not regard their amputation as a handicap and often participate in contact sports.

Table I—Clinical Results of Syme's Amputation

Finding	Amputation group, no. of patients		
	Traumatic (n = 35)	Dysvascular (n = 14)	Congenital (n = 6)
Stump pain	22	8	3
Phantom pain	24	11	3
Prosthetic users (full time)	35	13	6
End weight bearing (without prosthesis)	18	2	4
Shape of stump			
Bulbous	30	10	4
Round	3	2	1
Conical	—	2	—
Flat	2	—	1
Mobility of stump			
Grade 1	7	5	0
2	16	4	2
3	11	4	3
4	1	1	1
Functional result			
Good	24	10*	5
Fair	6	2	1
Poor	5	1	0

*11 amputations.

Conclusions

Our findings suggest that a functional Syme's amputation depends more on good prosthetic fitting than on meticulous technical detail. Poor technique is inexcusable, but we think too much emphasis has been placed on technical imperfections as the cause of failure.

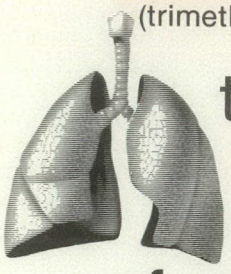
In patients with dysvascular limbs, Syme's amputation cannot be recommended because of the high failure rate. Better preoperative assessment may help to predict the probability of success in these patients. For traumatic lesions of the foot, consideration should be given to early elective Syme's amputation in preference to multiple procedures to preserve it. The risk of a more proximal amputation increases with the number of foot procedures performed.

References

1. SYME J: Amputation at the ankle-joint. *Lond Edinb Month J Med Sci* 1843; 3: 93–6
2. LAMB R: Present evaluation of the Syme amputation. *Am J Surg* 1958; 95: 688–92
3. BAKER GC, STABLEFORTH PG: Syme's amputation. A review of sixty- seven cases. *J Bone Joint Surg* [*Br*] 1969; 51: 482–7
4. DALE GM: Syme's amputation for gangrene from peripheral vascular disease. *Artif Limbs* 1961; 6: 44–51
5. MURDOCH G: Syme's amputation. *J R Coll Surg Edinb* 1976; 21: 15–30
6. SHELSWELL JH: Syme's amputation. *Lancet* 1954; 2: 1296–9
7. AITKEN GT: Surgical amputation in children. *J Bone Joint Surg* [*Am*] 1963; 45: 1735–41
8. DAVIDSON WH, BOHNE WH: The Syme amputation in children. *J Bone Joint Surg* [*Am*] 1975; 57: 905–9
9. EILERT RE, JAYAKUMAR SS: Boyd and Syme ankle amputations in children. *J Bone Joint Surg* [*Am*] 1976; 58: 1138–41
10. HARRIS RI: Syme's amputation; technical details essential for success. *J Bone Joint Surg* [*Br*] 1956; 38: 614–32
11. ALLDREDGE RH, THOMPSON TC: Technique of Syme amputation. *J Bone Joint Surg* 1946; 28: 415–26
12. WILSON PD: The Syme amputation. *Surg Clin North Am* 1921; 1: 711–28
13. HORNBY R, HARRIS R: Syme's amputation. Follow-up study of weight-bearing in sixty-eight patients. *J Bone Joint Surg* [*Am*] 1975; 57: 346–9
14. HUNTER GA, KENNARD AB: Mania operativa: an uncommon, unrecognized cause of limb amputation. *Can J Surg* 1982; 25: 92–3
15. WAGNER FW JR: Amputations of the foot and ankle. Current status. *Clin Orthop* 1977; 122: 62–9
16. SPITTLER AW, BRENNAN JJ, PAYNE JW: Syme amputation performed in 2 stages. *J Bone Joint Surg* [*Am*] 1954; 36: 37–42

Bactrim™ Roche®

(trimethoprim plus sulfamethoxazole)



the drug of **first choice** in the treatment of *pneumocystis carinii* pneumonitis is **a solution for serious infections**

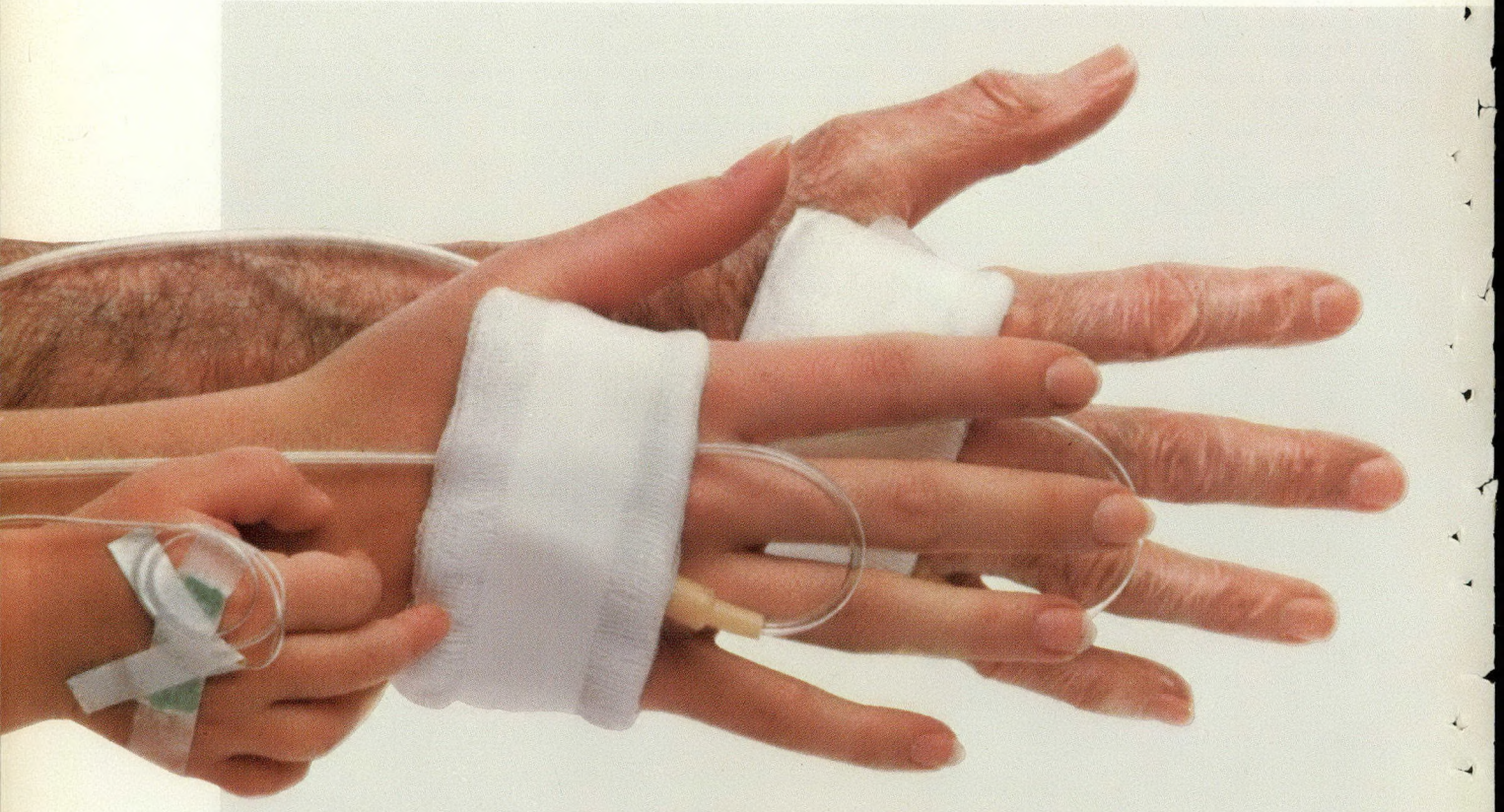
'Bactrim' Solution for Infusion has also produced dramatic results in

- severe urinary tract infections
- septicemia
- meningitis

TMP-SMX "...has particularly been useful against organisms that are resistant to ampicillin or are resistant to the first and second generation cephalosporins, and it has been very active against certain organisms that appear to be resistant to pretty much everything we have ..."(1)

An important weapon when aggressive antibacterial measures are required.

ROCHE®



For prescribing information see page 251

R.G. KEITH, MD, FRCS, FRCSC;* S.H. KESHAVJEE, MD;* N.R. KERENYI, MD, FRCPC†

Neuropathology of Chronic Pancreatitis in Humans

To investigate the pathogenesis of pain in chronic pancreatitis, tissue resected from 50 patients with this condition was examined by light microscopy. An examiner, blinded to clinical and pathological data, graded perineural fibrosis, inflammation and the composition of inflammatory infiltrate in 2132 separate perineural fields.

Correlation of perineural fibrosis and inflammation grading with alcohol ingestion and pain severity was insignificant. Pain severity did correlate with the timing of alcohol consumption. Although calcification significantly affected pain severity, the status of duct dilatation was not significant.

Eosinophils were observed in disproportionate numbers in the perineural infiltrate. The correlation of percentage eosinophilic infiltrate and pain severity was highly significant. Timing of alcohol consumption also correlated significantly with the percentage eosinophilic infiltration.

As eosinophils are known to be cytotoxic and injurious to tissue by liberation of enzymes through degranulation, the findings of this study suggest that the pain of chronic pancreatitis may be mediated by perineural eosinophils, through a chemotactic mechanism involving alcohol.

Afin de rechercher la pathogénèse de la douleur dans la pancréatite chronique, on a examiné au microscope optique les tissus réséqués de 50 patients affligés de cette maladie. Ignorant des données cliniques et pathologiques, un examinateur a évalué la fibrose périneurale, l'inflammation et la composition de l'infiltrat inflammatoire dans 2132 champs périneuraux.

La corrélation entre la fibrose périneurale et l'inflammation d'une part, et l'ingestion d'alcool et l'intensité de la douleur d'autre part, s'est avérée sans importance. L'intensité de la douleur s'est montrée toutefois reliée au moment de la prise d'alcool. Si la calcification avait une influence significative sur l'intensité de la douleur, le degré de la dilatation du canal pancréatique était sans importance.

Des éosinophiles ont été observés dans un nombre disproportionné d'infiltrats périneuraux. La corrélation entre le pourcentage des infiltrats éosinophiles et l'intensité de la douleur était hautement significative. Le moment de la prise d'alcool a aussi montré une corrélation importante avec le pourcentage des infiltrations éosinophiles.

Puisqu'on sait que les éosinophiles sont cytotoxiques et lèsent les tissus par une libération d'enzymes consécutive à un processus de dégranulation, les résultats de cette étude montrent que les éosinophiles périneuraux sont susceptibles de participer à la douleur de la pancréatite chronique par un mécanisme chimiotaxique impliquant l'alcool.

*From the *Department of Surgery and †Department of Pathology, University of Toronto, and Sunnybrook Medical Centre, Toronto, Ont.*

Presented at the 7th annual meeting of the Canadian Association of General Surgeons, Montreal, PQ, Sept. 11, 1984, held in conjunction with the 53rd annual meeting of the Royal College of Physicians and Surgeons of Canada

Accepted for publication Nov. 27, 1984

Reprint requests to: Dr. Roger G. Keith, Department of Surgery, Sunnybrook Medical Centre, 2075 Bayview Ave., Toronto, Ont. M4N 3M5

Although pain is the predominant clinical feature of chronic pancreatitis, its pathogenesis is poorly understood. Pain relief may be obtained following various surgical procedures that treat different pathologic effects of chronic inflammation, but complete freedom from pain is achieved only by total pancreatectomy.[1-7]

Various abnormalities of the pancreatic ducts are recognized in chronic pancreatitis.[8] Painless pancreatitis occurs with gross dilatation of the ducts, while severe pain may accompany chronic pancreatitis without dilatation. The severity of the pain does not correlate with duct dilatation, strictures or obstruction.[9-12]

Bradley[13] reported elevated pressures in dilated ducts studied during surgery for chronic pancreatitis. He suggested that the pain correlated with increased hydrostatic pressure. However, normal pressures have been recorded in patients with chronic pancreatitis with dilated ducts, and manometric values in patients with chronic pancreatitis equalled those in normal patients.[14,15] Pancreatic stimulation tests do not increase pancreatic pain in many subjects with chronic pancreatitis.[16]

Painful pancreatitis occurs without calcification in up to 50% of patients. Ammann and colleagues[17] described decreased severity of pain with accompanying increased calcification during long-term follow-up of patients with chronic pancreatitis. It is doubtful that calcification alone causes pancreatic pain.

Sensory afferent fibres leaving the pancreas follow the sympathetic nerves, which pass through the celiac ganglia and splanchnic nerves. Celiac ganglionectomy and anesthetic nerve blocks abolish pancreatic pain.[6,7] Apparently, neural components are involved in transmitting pain associated with chronic pancreatitis.

This study was conducted to examine the histopathology of chronic pancreatitis, with particular reference to the neural elements within the gland. To evaluate the mechanism of pain, clinical features of the disease were correlated with histologic observations.

Patients and Methods

Tissue obtained from 50 patients who underwent pancreatic resection or decompression was examined histologically by

a single observer, blinded to clinical and gross pathological data. In all, 2132 separate perineural fields were examined. One perineural field was represented by a × 150 magnification surrounding at least one nerve fibril within the pancreatic tissue (Fig. 1). Recordings were made of the distribution and grading of fibrosis and the distribution, grading and cell composition of the inflammatory infiltrate and the findings were compared with those of control tissue made of historically normal pancreatic tissue and pancreas obtained at autopsy from trauma victims.

Gross pathologic data was previously recorded for each patient, based on preoperative radiologic examination, operative examination and gross pathological examination. Documentation in each case included tissue sample sites, pancreatic duct status and the presence of calcification. These data were withheld from the histologic examiner.

Fibrosis was graded as follows: grade 1 — a minimal excess of loosely arranged fibrous tissue in direct contact with the perineurium; grade 2 — more densely arranged fibrous tissue surrounding the nerve fibril, usually associated with an increased inflammatory component (Fig. 2); grade 3 — excessive perineural proliferation of fibrous tissue, widely separating the acinar lobules (Fig. 3).

The perineural inflammatory infiltrate was graded according to the cellular density of the inflammation: grade 1 — minimal infiltration by occasional lymphocytes and histiocytes in the perineural region; grade 2 — moderate density of cellular infiltration (Fig. 2); grade 3 — marked infiltration of the perineural field (Fig. 3); grade 4 — infiltration of the entire perineural field.

Clinical information was previously recorded for each patient. Pain was graded according to outpatient records, pharmaceutical prescription review and inhospital records. Grading of pain was tabulated as the mean number of 30-mg codeine equivalents required every 24 hours. Alcohol intake was recorded from the patient history, referring physician history and history by family members. Intake of alcohol greater than 50 g/d was considered significant. The length of abstinence before tissue sampling was used to compute an alcohol grading score. Total abstinence was graded 0, recent alcohol intake was given a maximum grade of 30. Grading between 30 and 0 depended on quantity consumed and duration of abstinence before operation. The score was biased towards the duration of abstinence preoperatively, with each month of abstinence lowering the score by one point.

The status of the pancreatic duct was compared to the mean grading of pain severity and to the composition of the inflammatory infiltrate using the paired Student's *t*-test. The presence or absence of calcification was similarly compared. Fibrosis grading and inflammatory infiltrate grading were compared separately to grading of severity of pain by calculating correlation coefficients; the significance of each r value was determined from probability tables. Similarly, correlation coefficients were determined comparing alcohol scoring with severity of pain, composition of inflammatory infiltrate with severity of pain and composition of infiltrate with alcohol scoring.

Where correlation coefficients were found to be significant, a linear relationship was plotted by calculating the slope and intercept values for the data under consideration. The linear relationship was illustrated graphically.

Findings

The histopathologic features were equivalent in the same subject, regardless of the sites from which the tissue samples were obtained. Consistently, all histologic examinations showed that the fibrosis and inflammation were distributed in the interlobular planes. There was minimal

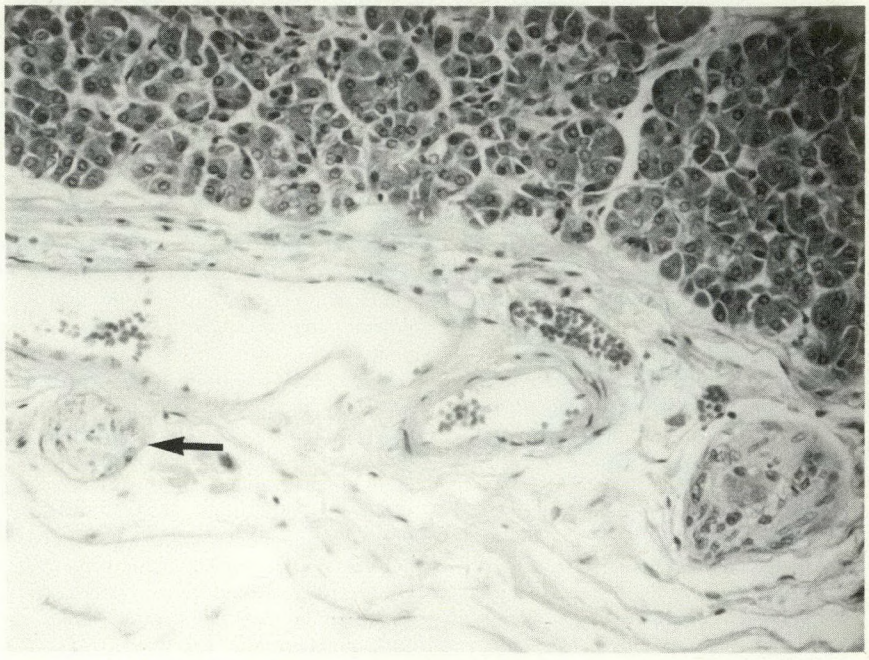


FIG. 1—Photomicrograph of normal pancreas illustrating one perineural field around nerve fibril (arrow) (hematoxylin and eosin, reduced by 29% from × 150).

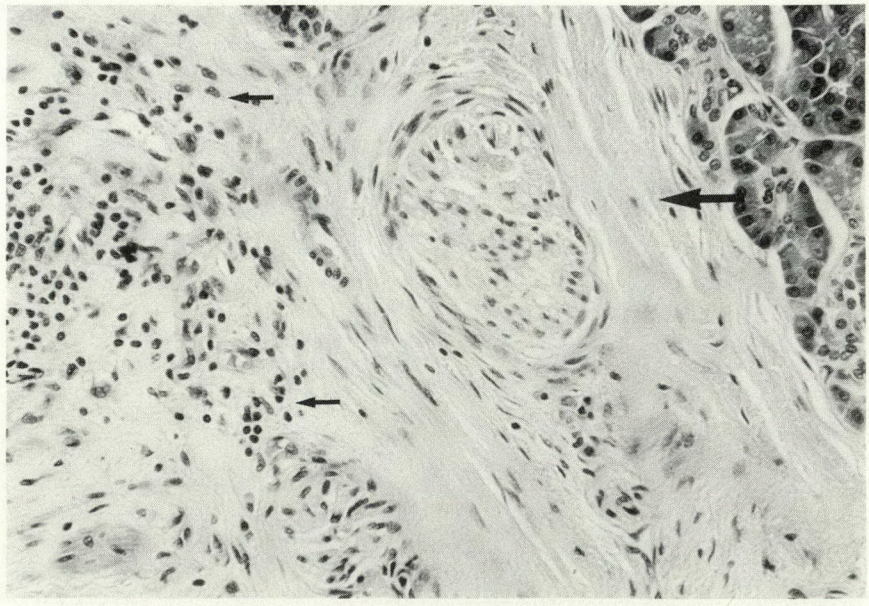


FIG. 2—Perineural field illustrating grade 2 fibrosis (large arrow) and grade 2 inflammation (small arrows) (hematoxylin and eosin, reduced by 32% from × 150).

intralobular fibrosis or inflammation within preserved acinar tissue (Figs. 2 and 3). No inflammation or fibrosis was noted around intralobular ducts. Fibrosis was continuous in the interlobular plane, surrounding neural and vascular structures. However, inflammatory infiltrate was precisely restricted to perineural locations (Fig. 3).

The pancreatic duct was considered to be dilated when preoperative pancreatography, operative pancreatography or gross pathological examination revealed a duct diameter greater than 1.0 cm. When the mean grading of pain severity was compared between 19 subjects with dilated pancreatic ducts and 31 with non-dilated ducts, the difference was not significant (mean 30-mg codeine equivalents daily, 3.9 and 4.4, respectively, $p > 0.2$).

There was a significant correlation ($r = 0.34$, $p < 0.02$) between alcohol scores and the severity of pain. The linear relation between these two features was plotted (Fig. 4). Alcohol scores were well distributed with 13 abstainers and 13 subjects consuming more than 50 g of alcohol daily, within 6 months of operation. Eleven subjects had painless pancreatitis, while the remainder required from 2 to 20 codeine equivalents daily.

Calcification of the pancreas was noted in the parenchyma and within ducts by pancreatography, operative observation or pathological examination. The mean severity of pain was compared between 24 patients of the sample group of 50 who did not have calcification (2.83 ± 3.4 [standard error] codeine equivalents) and the remainder who had documented calcification of the gland (5.52 ± 4.0 codeine equivalents). The difference was significant ($p < 0.02$).

Fibrosis was abnormal in all cases compared with controls. Fibrosis was graded for each perineural field and was consistent throughout all samples for each case; thus, median fibrosis grading could be recorded for each subject. Grade 3 fibrosis was recorded in the majority of examinations (64%), grade 1 in 8% and grade 2 in 28%. Correlation between grading of fibrosis and mean grading of pain severity was not significant ($r = 0.123$, $p > 0.1$).

As was observed with fibrosis, the grading of the perineural inflammatory infiltrate remained consistent in all samples from the same patient. It was only found around nerve fibrils in the interlobular plane; no infiltrate was noted in the acinar or periductular tissues (Figs. 2, 3, 5 and 6).

The majority of patients (76%) had grade 2 inflammation (Table I). None of the perineural fields examined showed grade 4 inflammation. Correlation between the grading of inflammation and the severity of pain was not significant ($r = 0.179$, $p > 0.1$).

When the composition of the inflammatory infiltrate was analysed for each

FIG. 3—Perineural field illustrating grade 3 inflammation restricted to perineural region (arrows) and grade 3 fibrosis (hematoxylin and eosin, reduced by 32% from × 60).

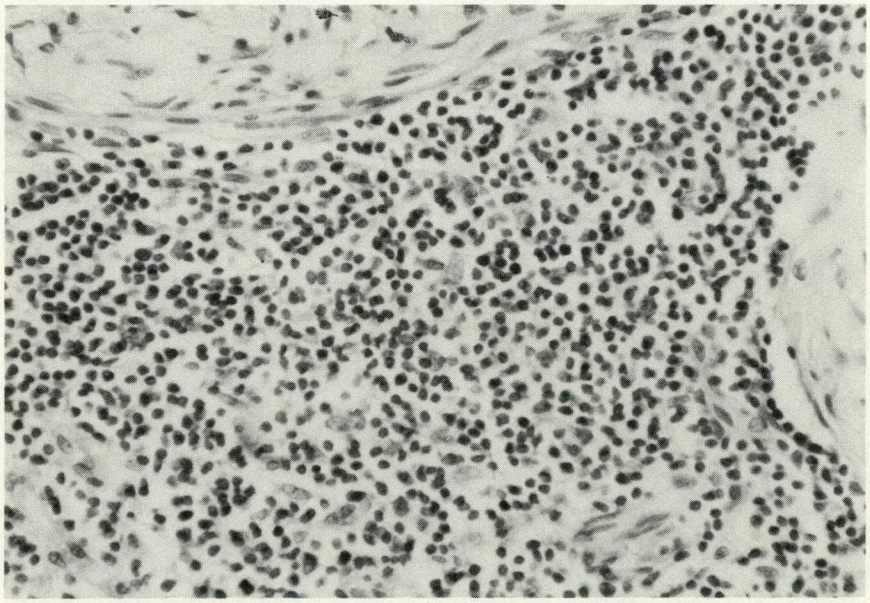


FIG. 5—Perineural infiltrates were composed of lymphocytes, histiocytes, occasional plasma cells and neutrophils (hematoxylin and eosin, reduced by 32% from × 250).

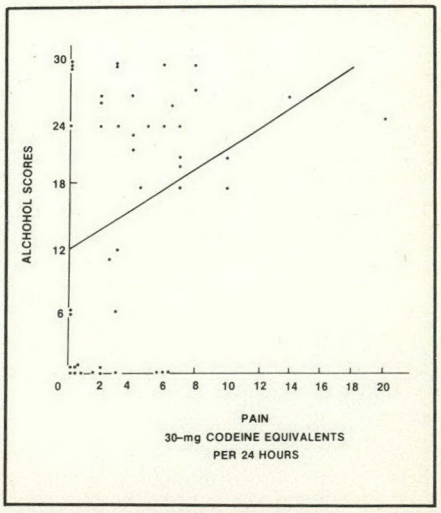


FIG. 4—Significant correlation ($r = 0.34$, $p < 0.02$) between alcohol score and pain severity.

Table I—Grading of Perineural Inflammatory Infiltrate

Grade	Description	% of samples
1	Minimal	10
2	Moderate	76
3	Marked	14
4	Severe	0

perineural field, the chronic infiltrate was noted to be composed predominantly of lymphocytes, histiocytes with occasional plasma cells and neutrophils (Fig. 5). A startling observation was the disproportionate numbers of eosinophils present in the perineural infiltrate (Fig. 6). This has not been reported before. With higher grades of inflammation, a correspondingly greater number of eosinophils was observed. The presence of the eosinophils bore no relation to the size of the nerve fibril, or to the number of fibrils in each perineural field. The eosinophils were distributed close to the nerve fibril and on several examinations the cells were noted within the perineurium. Several scattered observations were recorded, suggesting degranulation of the eosinophils (Fig. 7).

For each subject, the eosinophilic component of the infiltrate was analysed in two ways. Percentage eosinophilic concentration documented the total number of perineural fields with eosinophils compared with the total number of perineural fields examined. The eosinophil density was the total number of eosinophils per total number of perineural fields with an eosinophilic component. The density number and the percentage eosinophilic infiltration were similar for each subject; the percentage eosinophilic infiltration was the index chosen for analysis.

On analysis of the mean grading of pain severity and percentage eosinophilic infiltration, the correlation coefficient was highly significant ($r = 0.56$, $p < 0.001$). The slope and intercept were calculated for the data and the linear relation was illustrated graphically (Fig. 8).

Similarly, the relation between the alcohol score and the percentage eosinophilic infiltration was calculated. The correlation coefficient was again significant ($r = 0.44$, $p < 0.01$) (Fig. 9).

The relation between the pancreatic duct status and the eosinophilic composition of the perineural infiltrate was analysed by comparing percentage eosinophilic infiltration between the 19 patients with dilated and 31 with nondilated ducts. There was no significant difference (mean eosinophilic infiltration 30% versus 43.2%, $p > 0.1$).

When the 26 subjects with pancreatic calcification were compared with the 24 patients without, no significant difference was noted in the mean percentage eosinophilic infiltration (46.4% versus 31.6%, $p > 0.1$).

Discussion

Changes in pancreatic secretion and ultrastructure due to long-term consumption of alcohol are well recognized. Variable patterns of duct dilatation and stricture have been described in chronic alcoholic pancreatitis.[8-10] Chronic fibrosing pancreatitis does not always pro-

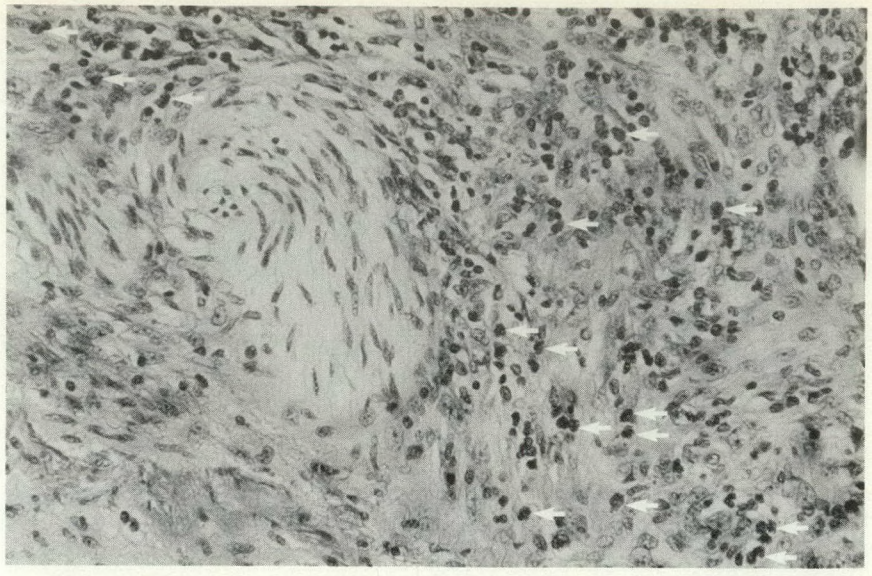


FIG. 6—Disproportionate numbers of eosinophils were observed in perineural infiltrate (arrows) (hematoxylin and eosin, reduced by 32% from × 250).

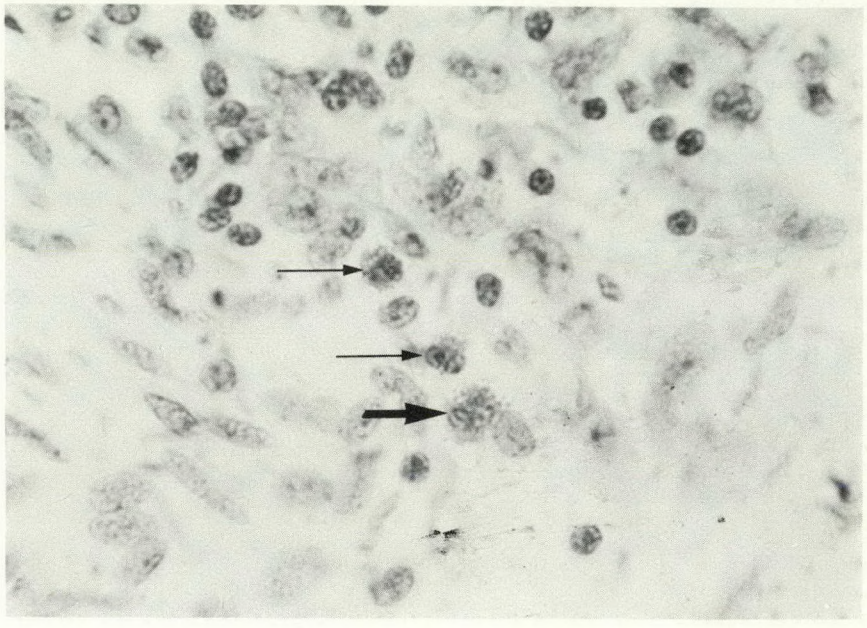


FIG. 7—Degranulation of eosinophils (arrows) (hematoxylin and eosin, reduced by 32% from × 500).

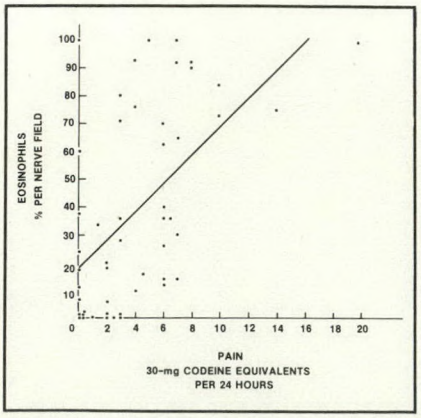


FIG. 8—Significant correlation ($r = 0.56$, $p < 0.001$) between percentage eosinophilic infiltration and pain severity.

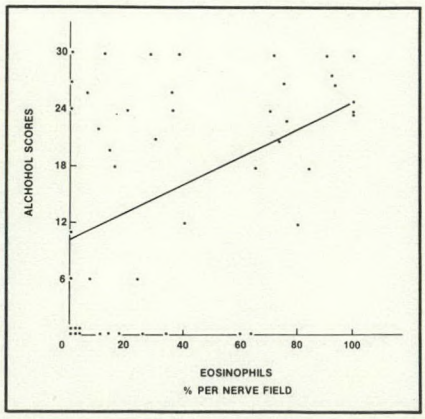


FIG. 9—Significant correlation ($r = 0.44$, $p < 0.01$) between alcohol score and percentage eosinophilic infiltration.

duce duct dilatation. Noronha and coworkers[18] have described progressive perilobular fibrosis and variable acinar atrophy in association with long-term alcohol consumption. Calculus formation in chronic calcific pancreatitis has been extensively investigated by Sahel and Sarles,[19] since changes in pancreatic protein secretion were identified in man and experimental animals, following long-term alcohol intake. The recent identification of the pancreatic stone protein has consolidated the theory that abnormal pancreatic secretion leads to calculus formation in chronic calcific pancreatitis.[20,21] These morphologic and secretory abnormalities are accepted sequelae of long-term alcohol ingestion. Our study confirmed universal interlobular fibrosis in all specimens examined. However, it failed to document any correlation of pain severity with the grading of perineural fibrosis. Similarly, it did not differentiate grading of pain based on pancreatic duct dilatation or stricture.

Pancreatic calcification was present in only half our cases. Although pain increased substantially with calcific pancreatitis, whether calcification alone can produce pain is controversial. From our study, it is important to recognize the lack of significant difference in eosinophilic composition of the perineural infiltrate comparing calcific pancreatitis to noncalcific pancreatitis. This suggests that the eosinophil is not responsible for increased pain associated with calcification.

The specific perineural location of the chronic inflammatory infiltrate observed in all specimens has not been documented previously. The chemotactic factors responsible for this localization are unknown. Grading of the inflammatory infiltrate (cellular density) did not correlate significantly with the grading of pain severity. Discovery of the previously unrecognized eosinophilic composition of the infiltrate prompted a measurement of percentage eosinophilic infiltration for each perineural field. Correlation of previously graded clinical features of pain severity and alcohol score was found to be significant (Fig. 4), as it was also between the eosinophilic infiltrate and pain severity. Moreover, the eosinophilic infiltration correlated significantly with the alcohol score, which was biased towards the timing of recent alcohol consumption. There was no significant relation between eosinophilic infiltration and pancreatic duct morphology.

From analysis of our data, the eosinophilic component of the perineural infiltrate appears to be involved in the pathogenesis of pain in chronic pancreatitis.

Although the role of the eosinophil is poorly understood, it is believed to have a physiologic and pathologic role in collagen degradation.[22] An eosinophilic chemotactic factor has been identified that will attract and enhance the action of the eosinophil.[23] Its subsequent cytotoxicity depends upon antibody binding.[24] The surface-binding proteins of the eosinophil likely combine with the immunoglobulins.[25] Cell and tissue injury are mediated by eosinophilic release of eosinophil cationic protein and major basic protein. Recent investigations have suggested that new proteins are released from the eosinophil, with varying enzyme action.[26] Pertinent to this study is a recent description of an eosinophilic protein that is injurious to nerve tissue, the eosinophil-derived neurotoxin.[27]

Although the main area of interest in the cytotoxic action of the eosinophil concerns parasitology, spontaneous lung parenchymal cell and collagen matrix damage by eosinophils has recently been reported.[28] Our study may suggest that chemotactic factors in the interlobular spaces, specifically near nerve fibrils, attract an eosinophil-rich inflammatory infiltrate. It is also suggested by the significant clinical correlation that such a mechanism is alcohol-related. Degranulation of the eosinophil (Fig. 7) results in enzyme activation that may be responsible for the nerve-mediated pain mechanism in chronic pancreatitis.

References

1. KEITH RG, SHEPPARD RH, SAIBIL FG, BROW JR: Resection for chronic alcoholic pancreatitis. *Can J Surg* 1981; 24: 119–24
2. FREY CF, CHILD CG, FRY W: Pancreatectomy for chronic pancreatitis. *Ann Surg* 1976; 184: 403–13
3. ECKHAUSER FE, STRODEL WE, KNOL JA, HARPER M, TURCOTTE JG: Near-total pancreatectomy for chronic pancreatitis. *Surgery* 1984; 96: 599–607
4. GALL FP, MÜHE E, GEBHARDT C: Results of partial and total pancreaticoduodenectomy in 117 patients with chronic pancreatitis. *World J Surg* 1981; 5: 269–75
5. WHITE TT, KEITH RG: Long term follow-up study of fifty patients with pancreaticojejunostomy. *Surg Gynecol Obstet* 1973; 136: 353–8
6. WHITE TT, SLAVOTINEK AH: Results of surgical treatment of chronic pancreatitis. Report of 142 cases. *Ann Surg* 1979; 189: 217–24
7. MALLET-GUY PA: Late and very late results of resections of the nervous system in the treatment of chronic relapsing pancreatitis. *Am J Surg* 1983; 145: 234–8
8. NAGATA A, HOMMA T, TAMAI K, UENO K, SHIMAKURA K, OGUCHI H, FURUTA S, ODA M: A study of chronic pancreatitis by serial endoscopic pancreatography. *Gastroenterology* 1981; 81: 884–91
9. SARLES H, SAHEL J: Pathology of chronic calcifying pancreatitis. *Am J Gastroenterol* 1976; 66: 117–39
10. NAKAMURA K, SARLES H, PAYAN H: Three-dimensional reconstruction of the pancreatic ducts in chronic pancreatitis. *Gastroenterology* 1972; 62: 942–9
11. GRODSINSKY C, SCHUMAN BM, BLOCK MA: Absence of pancreatic duct dilation in chronic pancreatitis: surgical significance. *Arch Surg* 1977; 112: 444–9
12. BORNMAN PC, MARKS IN, GIRDWOOD AH, CLAIN JE, NARUNSKY L, CLAIN DJ, WRIGHT JP: Is pancreatic duct obstruction or stricture a major cause of pain in calcific pancreatitis? *Br J Surg* 1980; 67: 425–8
13. BRADLEY EL III: Pancreatic duct pressure in chronic pancreatitis. *Am J Surg* 1982; 144: 313–6
14. KEITH RG: Effect of a low fat elemental diet on pancreatic secretion during pancreatitis. *Surg Gynecol Obstet* 1980; 151: 337–43
15. NOVIS B, BORNMAN P, GIRDWOOD A, MARKS I: Pancreatico-biliary manometry in patients with chronic pancreatitis (abstr). *Scand J Gastroenterol* 1982; 17 (suppl): 320
16. WORNING H: Chronic pancreatitis: pathogenesis, natural history and conservative treatment. *Clin Gastroenterol* 1984; 13: 871–94
17. AMMANN RW, AKOVBIANTZ A, LARGIADER F, SCHUELER G: Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 1984; 86(5 pt 1): 820–8
18. NORONHA M, BORDALO O, DREILING DA: Alcohol and the pancreas. II. Pancreatic morphology of advanced alcoholic pancreatitis. *Am J Gastroenterol* 1981; 76: 120–4
19. SAHEL J, SARLES H: Modifications of pure human pancreatic juice induced by chronic alcohol consumption. *Dig Dis Sci* 1979; 24: 897–905
20. MULTIGNER L, DE CARO A, LOMBARDO D, CAMPESE D, SARLES H: Pancreatic stone protein, a phosphoprotein which inhibits calcium carbonate precipitation from human pancreatic juice. *Biochem Biophys Res Commun* 1983; 110: 69–74
21. GUY O, ROBLES-DIAZ G, ADRICH Z, SAHEL J, SARLES H: Protein content of precipitates present in pancreatic juice of alcoholic subjects and patients with chronic calcifying pancreatitis. *Gastroenterology* 1983; 84: 102–7
22. BASSETT EG: Eosinophils and connective tissue catabolism (C). *Biochem J* 1983; 213: 769–70
23. VADAS MA, NICOLA NA, METCALF D: Activation of antibody-dependent cell-mediated cytotoxicity of human neutrophils and eosinophils by separate colony-stimulating factors. *J Immunol* 1983; 130: 795–9
24. HALLAM C, PRITCHARD DI, TRIGG S, EADY RP: Rat eosinophil-mediated antibody-dependent cellular cytotoxicity: investigations of the mechanisms of target cell lysis and inhibition by glucocorticoids. *Clin Exp Immunol* 1982; 48: 641–8
25. THORNE KJ, FRANKS D: Surface proteins of the human eosinophil. I. Isolation of eosinophil IgG binding proteins. *Clin Exp Immunol* 1984; 56: 464–72
26. PETERSON CG, VENGE P: Purification and characterization of a new cationic protein — eosinophil protein-X (EPX) — from granules of human eosinophils. *Immunology* 1983: 50: 19–26
27. DURACK DT, ACKERMAN SJ, LOEGERING DA, GLEICH GJ: Purification of human eosinophil-derived neurotoxin. *Proc Natl Acad Sci USA* 1981; 78: 5165–9
28. DAVIS WB, FELLS GA, SUN XH, GADEK JE, VENET A, CRYSTAL RG: Eosinophil-mediated injury to lung parenchymal cells and interstitial matrix. A possible role for eosinophils in chronic inflammatory disorders of the lower respiratory tract. *J Clin Invest* 1984; 74: 269–78

BOOKS RECEIVED

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

Advances in Gastrointestinal Surgery. From the Forty-seventh Annual Continuation Course in Surgery, University of Minnesota Medical School, Minneapolis. Edited by John S. Najarian and John P. Delaney. 640 pp. Illust. Year Book Medical Publishers, Inc., Chicago, 1984. Price not stated. ISBN 0-8151-6336-3.

Clinical Neurosurgery. Volume 31. Proceedings of the Congress of Neurological Surgeons, Chicago, Illinois, 1983. 592 pp. Illust. Williams & Wilkins, Baltimore, 1984. $52 (US). ISBN 0-683-02026-9.

Fluids and Electrolytes in the Surgical Patient. 3rd ed. Carlos Pestana. 245 pp. Illust. Williams & Wilkins, Baltimore, 1985. $18.95 (US). ISBN 0-683-06861-X.

Genitourinary Cancer. Contemporary Issues in Clinical Oncology, Volume 5. Edited by Marc B. Garnick. 280 pp. Illust. Academic Press Canada, Don Mills, Ont., 1985. $55.50. ISBN 0-443-08350-9.

continued on page 226

Nature's Gentle Persuasion

Parke-Davis Glycerin Suppositories

A non-systemic laxative for the gentle, yet timely evacuation of the lower bowel within 15 minutes to 1 hour.

Its natural ingredient makes it a preferred laxative for many patients, particularly pregnant women, seniors and children.

Parke-Davis Glycerin Suppositories are the laxative often chosen by physicians who require fast yet gentle relief in a non-systemic form.

Available in adult and child forms. For best results, insert and allow to melt naturally.

PARKE-DAVIS

Parke-Davis Canada Inc., Scarborough, Ontario

PAAB CCPP *Reg. T.M. Parke, Davis & Company Parke-Davis Canada Inc., auth. user PMAC

For prescribing information see page 231

BRIAN W. LOGGIE, MD;* G. HAUER-POLLACK, M SC;
E. JOHN HINCHEY, MD, M SC, FRCSC, FACS

Influence of Splenectomy on Lethal Effects of Pneumococcal Infection

To determine whether the splenectomized host is more sensitive to the toxic effects of pneumococcal infection and whether the known clearance defect accounts for the early, increased mortality seen in postsplenectomy infection, the authors studied 8-week-old C57B1 mice. They were divided into two groups: seven control nonsplenectomized mice and six splenectomized mice. All animals were inoculated intravenously with 10^3 colony forming units of *Streptococcus pneumoniae*. Microaliquots of blood were drawn from the tail of all mice into sterile, heparinized, capillary tubes at 1, 4, 8 and 16 hours. Blood bacteria were quantitated using a drop dilution method. The time to death was recorded. A form of survival analysis using the Cox proportional hazards model was performed on the data.

The infection was uniformly fatal. An early decrease in the numbers of blood bacteria was seen in nonsplenectomized mice followed by a logarithmic linear increase. In splenectomized mice, there was early rapid bacterial growth greater than that in control mice. Splenectomized mice died earlier than control mice ($p < 0.05$ at 24 hours, Fisher's exact test). The bacterial count had a highly significant effect upon mortality overall ($p = 0.0017$). A function describing the risk of dying versus bacterial numbers was generated and was the same for both groups.

The splenectomized host does not appear to be more susceptible to the toxic effects of pneumococcal infection. Early mortality in bacteremic pneumococcal infection can be attributed to impaired bacterial clearance alone.

Cette étude a été réalisée afin de vérifier si le sujet splénectomisé est davantage sensible aux effets toxiques de l'infection pneumococcique et si le défaut de clairance que l'on connaît, explique l'augmentation de la mortalité précoce post-splénectomie. Des souris C57B1 âgées de 8 semaines ont été réparties en deux groupes, soit sept souris témoins non splénectomisées et six souris splénectomisées. Tous les animaux ont reçu par voie intraveineuse 10^3 unités formant des colonies de *Streptococcus pneumoniae*. Des micro-aliquotes de sang ont été prélevées de la veine caudale des souris à l'aide de tubes capillaires héparinés stériles après 1, 4, 8 et 16 heures. La numération des bactéries du sang a été faite par la méthode de la dilution de la goutte. Le temps du décès a été enregistré. Une forme d'analyse de survie reposant sur le modèle des risques proportionnels de Cox a été effectuée sur les données.

Dans tous les cas, l'infection fut mortelle. Chez les souris non splénectomisées, une diminution précoce du nombre de bactéries du sang fut suivie d'une augmentation linéaire logarithmique. Chez les souris splénectomisées, on observa une croissance bactérienne précoce plus rapide que chez les souris témoins. Les souris splénectomisées sont mortes plus tôt que les témoins ($p < 0.05$ à 24 heures, test de probabilité exacte de Fisher). La numération bactérienne a montré un effet hautement significatif sur la mortalité globale ($p = 0.0017$). Une équation décrivant le risque de mortalité en fonction de la numération bactérienne fut dérivée; celle-ci était la même pour les deux groupes.

Les sujets splénectomisés ne paraissent pas avoir une sensibilité accrue aux effets toxiques de l'infection pneumococcique. La mortalité précoce rattachée à la bactérie pneumococcique peut être attribuée au seul défaut de la clairance bactérienne.

The syndrome of overwhelming postsplenectomy infection has been based predominantly on case reports of severe pneumococcal infections occurring in splenectomized patients. The patients are often young and in apparent good health when mild prodromes develop that progress rapidly to severe illness and early death.[1] Features of the illness include the Waterhouse–Friderichsen syndrome (bilateral adrenal hemorrhage), which has frequently been described, often in association with disseminated intravascular coagulation.[2-4] These lesions have usually been attributed to infections caused by gram-negative endotoxin-producing organisms such as meningococci. Pneumococci are gram-positive organisms and by definition do not produce endotoxin.

Experimental studies have shown that after splenectomy, bacterial clearance is impaired.[5] We have hypothesized that, in addition to the known defect of bacterial clearance, the clearance of toxins or bacterial degradation products may also be impaired. Theoretically, such a defect could synergistically contribute to the patient's early death and might account for some of the unusual clinical manifestations noted in the course of overwhelming postsplenectomy infection. If this hypothesis is true, then it is expected that the absence of the spleen would confer an additional disadvantage on the splenectomized host, synergistic with the known clearance defect and hastening a fatal outcome. If this hypothesis is false, then no difference in susceptibility to the fatal effects of pneumococcal infection is expected and the fatal bacterial load will be similar for splenectomized and nonsplenectomized animals.

We can predict that the fatally infected splenectomized host will die earlier than the fatally infected normal host on the basis of differences in ability to clear bacteria. However, by closely following fatal

From the Department of Surgery and Department of Epidemiology and Health, McGill University, Montreal, PQ

Presented at the 7th annual meeting of the Canadian Association of General Surgeons, Montreal, PQ, Sept. 12, 1984, held in conjunction with the 53rd annual meeting of the Royal College of Physicians and Surgeons of Canada

**Research Fellow, Medical Research Council of Canada. Supported in part by the Fast Foundation*

Accepted for publication Jan. 29, 1985

Reprint requests to: Dr. E.J. Hinchey, Rm. 9857, Livingston Hall, Montreal General Hospital, 1650 Cedar Ave., Montreal, PQ H3G 1A4

bacteremic pneumococcal infections, it may be possible to determine whether an increased susceptibility to the lethal effects of pneumococcal infection exists. We have used a mouse model to examine our hypothesis.

Methods

Bacteria

Streptococcus pneumoniae, type III, smooth (ATCC), were maintained in frozen liquid subculture containing 20% glycerol. A vial was thawed and plated onto blood agar overnight (at 37°C in 5% carbon dioxide). Sidearm flasks containing sterile Todd–Hewitt broth were inoculated with fresh colonies and incubated in a standing rack. Growth was assessed by following changes in optical density at 600 nm. Organisms were harvested in the logarithmic growth phase and diluted in Hanks' balanced salt solution before inoculating the animals. The inoculum dose was confirmed by quantitative culture. Optimal virulence was assured by this technique as measured by the ability of small inocula to cause death after intraperitoneal injection as well by microscopic examination using India-ink counterstain, which demonstrated uniform encapsulation and chain-length.

Mice

Age-matched 8-week-old C57B1 mice were randomly assigned to two groups: seven control nonsplenectomized and six splenectomized mice. Splenectomies had been performed 3 weeks before inoculation and the mice had regained the weight lost postoperatively. All mice were inoculated intravenously with 1.6×10^3 colony forming units of *S. pneumoniae.* At 1, 4, 8 and 16 hours, microaliquots of blood were drawn from the tail vein of each mouse and placed into heparinized, precalibrated, sterile, glass capillary tubes. Serial dilutions in duplicate were plated to quantitate blood bacterial numbers accurately. The time to death was noted for each animal.

Statistical Analysis

Statistical differences were measured by Fisher's exact test for overall survival at 24 hours and Cox's proportional hazards regression analysis. The hazard function, the probability of dying at a certain time, conditional upon survival until that time, was first calculated using bacterial count as a covariate.

Results

By 24 hours, all splenectomized mice were dead, but only 29% of the nonsplenectomized mice (Fig. 1). This difference is statistically significant, $p < 0.05$ by Fisher's exact test.

When the course of infection in individual animals is correlated with the time to death (Fig. 2), the slope is steeper for splenectomized than for nonsplenectomized mice. The spectrum of bacterial clearance can be seen, showing that the earlier times of death in splenectomized mice correlate with the slopes of the bacterial counts.

The survival characteristics of the two groups were examined using Cox's proportional hazards model of regression analysis. The bacterial count had a highly significant effect upon the probability of death overall ($p = 0.0017$). When attempting to verify whether a factor other than the bacterial clearance defect could contribute to the earlier mortality of the splenectomized group, we added the group factor to the model containing the bacterial count factor. The effect of this was insignificant, indicating that nothing other than bacterial clearance appears to distinguish between the groups with respect to mortality. Moreover, there was no significant interaction between group and bacterial count, suggesting that the bacterial count affects the mortality of control and splenectomized animals in a similar fashion. Differences in bacterial clearance rates are sufficient to account for the difference in blood bacterial num-

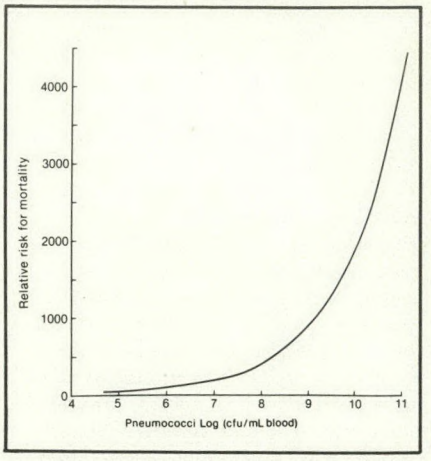


FIG. 3—Risk of death versus bacterial number. Using information from Fig. 2, risk of death was calculated for both groups, using Cox's proportional hazards model for survival analysis. Comparison of curves revealed no significant difference. Result of combined analysis is shown and demonstrates no inherent difference in risk of death, based on blood bacterial numbers between nonsplenectomized and splenectomized animals.

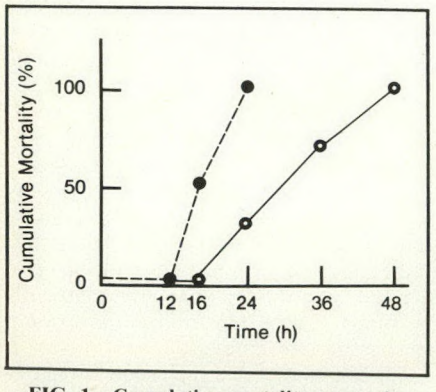


FIG. 1—Cumulative mortality versus time. Dashed line = splenectomized animals, solid line = nonsplenectomized animals. Difference in mortality is statistically significant ($p < 0.05$ at 24 hours, using Fisher's exact test).

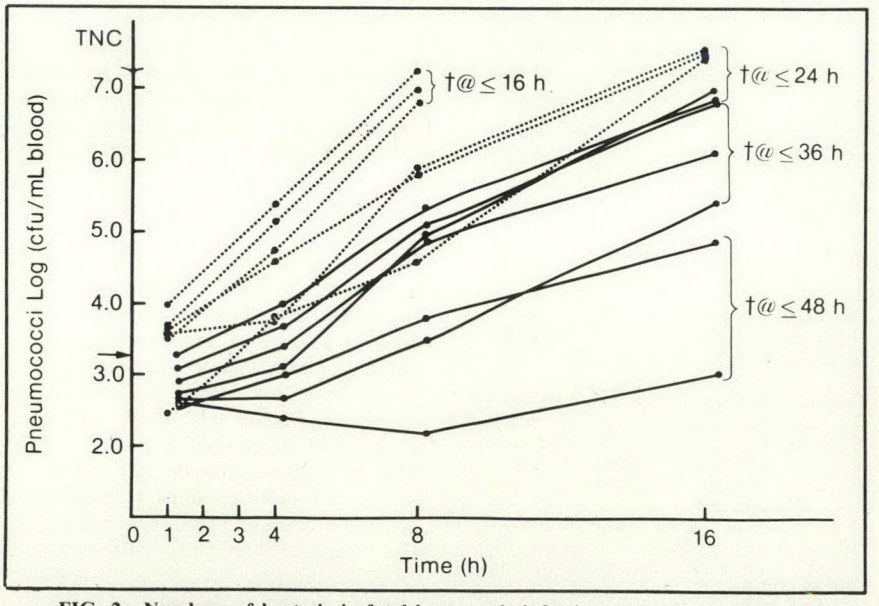


FIG. 2—Numbers of bacteria in fatal bacteremic infection and corresponding times to death. Logarithmic bacterial numbers (cfu/mL of blood, assay limit [⌣] 7.53) have been plotted versus time (h). Arrow on ordinate indicates initial bacterial inoculum corrected for circulating mouse blood volume. Each line represents single animal: dotted lines = splenectomized mice, solid lines = nonsplenectomized mice. Also included are approximate times to death (†), grouped according to whether animal was dead by less than or equal to 16, 24, 36 or 48 hours after inoculation. TNC = too numerous to count.

bers with time seen between the two groups. The risk of dying, plotted against bacterial numbers (Fig. 3), gave a curve that climbed exponentially and was identical for nonsplenectomized and splenectomized animals. This suggests that no inherent difference in susceptibility to the lethal effects of pneumococcal infection exists after splenectomy.

Discussion

That exotoxins and bacterial degradation products must play a role in the pathophysiology of pneumococcal infection seems certain but remains unproven. The pathophysiology of pneumococcal infection, especially those events leading to the death of the host, are poorly understood.[6] It has been shown clinically that death from pneumococcal infection can still occur after sterility has been achieved through the use of appropriate antibiotics. This fact has been attributed to circulating pneumococcal polysaccharide.[3] Acute anemia has been reported infrequently,[3,7] and it is not known whether this is due to elaboration of the hemolytic toxin, pneumolysin, or is related to something else.

In this study, fatally infected splenectomized mice died earlier and demonstrated a more rapid increase in numbers of bacteria than fatally infected nonsplenectomized animals. The risk of dying was determined solely by bacterial number and the calculated curve of relative risk for death was the same for both groups. This indicates that the fatal bacterial load was similar for both.

It is of interest that the introduction of antibiotics has not been shown to have a significant effect on early mortality from bacteremic pneumococcal infection.[8] Mortality remains high from pneumococcal infections in both the predisposed and the unpredisposed host. In a recent Canadian study,[9] there was a 41% mortality in adult patients without pre-existing underlying conditions and 43% in patients with known predisposing factors such as splenectomy. Our experimental findings are in keeping with these clinical observations since they suggest that outcome in the presence of an established infection is based on bacterial number and not on the presence or absence of splenectomy.

We conclude that the splenectomized host is not more susceptible to the lethal effects of pneumococcal infection. It seems, at least in the context of these experiments, that early mortality can be attributed to impaired pneumococcal clearance alone.

References

1. OAKES DD: Splenic trauma. *Curr Probl Surg* 1981; 18: 341–401
2. UL HAQUE A, MIN KW, FROM P, SONG J: Postsplenectomy pneumococcemia in adults. *Arch Pathol Lab Med* 1980; 104: 258–60
3. RYTEL MW, DEE TH, FERSTENFELD JE, HENSLEY GT: Possible pathogenetic role of capsular antigens in fulminant pneumococcal disease with disseminated intravascular coagulation (DIC). *Am J Med* 1974; 57: 889–96
4. TORRES J, BISNO AL: Hyposplenism and pneumococcemia. Visualization of *Diplococcus pneumoniae* in the peripheral blood smear. *Am J Med* 1973; 55: 851–5
5. BROWN EJ, HOSEA SW, FRANK MM: The role of the spleen in experimental pneumococcal bacteremia. *J Clin Invest* 1981; 67: 975–82
6. AUSTRIAN R: Pneumococcus: the first one hundred years. *Rev Infect Dis* 1981; 3: 183–9
7. RAMSAY LE, BOUSKILL KC: Fatal pneumococcal meningitis in adults following splenectomy: two case reports and a review of the literature. *J R Nav Med Serv* 1973; 59: 102–14
8. AUSTRIAM R, GOLD J: Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med* 1964; 60: 759–76
9. LAMOTHE F, DELAGE G, LAVERDIÈRE M, SAINT-ANTOINE P: Serogroups and serotypes of pneumococci in Montreal: correlations with age, outcome and indications for vaccination. *Can Med Assoc J* 1984; 130: 737–40

R. ARMOUR FORSE, MD, PH D, FRCSC; CAROL ROMPRE, RN; PAULINE CROSILLA, B SC; DEBORAH O-TUITT, B SC; BARBARA RHODE, B SC; HARRY M. SHIZGAL, MD, FACS, FRCSC

Reliability of the Total Lymphocyte Count as a Parameter of Nutrition

To evaluate the total lymphocyte count as a means of nutritional assessment, body composition studies (a proven method of nutritional assessment) and total lymphocyte determinations were performed simultaneously in 153 patients. The total lymphocyte count correlated poorly with both the body cell mass and the nutritional state measured by the Na_e to K_e ratio. For diagnosing malnutrition, the total lymphocyte count had a false-positive rate of 34% and a false-negative rate of 50%. In a group of 78 patients who received total parenteral nutrition for 2 weeks, the total lymphocyte count did not accurately reflect the nutritional changes. Due to its poor sensitivity and specificity, the total lymphocyte count is of no value as a measure of the nutritional state.

Afin d'évaluer l'intérêt de la numération lymphocytaire totale comme moyen d'établir l'état nutritionnel des patients, les auteurs ont pratiqué simultanément chez 153 d'entre-eux une étude de la composition corporelle (une méthode éprouvée pour établir l'état nutritionnel) et une numération lymphocytaire totale. Une faible corrélation a été observée entre la numération lymphocytaire totale et la masse cellulaire corporelle, de même qu'avec l'état nutritionnel mesuré par le rapport Na_e/K_e. Dans le diagnostic de la malnutrition, la numération lymphocytaire totale a eu un taux de faux résultats positifs de 34%, et 50% de faux négatifs. Chez un groupe de 78 patients qui ont reçu une alimentation parentérale totale pendant 2 semaines, la numération lymphocytaire totale n'a pas bien reflété les changements nutritionnels. Vu sa faible sensibilité et sa mauvaise spécificité, la numération lymphocytaire totale n'a aucune valeur comme mesure de l'état nutritionnel.

From the Department of Surgery, Royal Victoria Hospital and McGill University, Montreal, PQ

Presented at the 7th annual meeting of the Canadian Association of General Surgeons, Montreal, PQ, Sept. 11, 1984, held in conjunction with the 53rd annual meeting of the Royal College of Physicians and Surgeons of Canada

Accepted for publication Dec. 27, 1984

Reprint requests to: Dr. R.A. Forse, Rm. S6.24, Department of Surgery, Royal Victoria Hospital, 687 Pine Ave. W, Montreal, PQ H3A 1A1

An accurate assessment of a patient's nutritional status is important in both the application and evaluation of nutritional support. The association between malnutrition and an altered immune system is supported by a number of population surveys.[1,2] As a result, various parameters of the immune system have been employed as measures of nutrition in the hospitalized patient. One such application has been skin testing with recall antigens. This immune test has been used widely for nutritional assessment. We have recently reviewed this parameter and found that although the results of skin testing correlated well with malnutrition, the method did not have the sensitivity to measure the nutritional state of the individual patient.[3]

The total lymphocyte count has also been used clinically for nutritional assessment of the individual patient. This was based on earlier studies, showing that malnutrition caused a decrease in the total lymphocyte count and that nutritional support returned the count to normal.[4] Recent studies have not shown that the association between the nutritional state and the lymphocyte count is absolute.[5,6] Despite this, the lymphocyte count is still widely used and recommended for nutritional assessment in hospitalized patients.[7] This study was undertaken to determine the validity of using the total lymphocyte count as a measure of nutrition.

Patients and Methods

On 313 separate occasions, data were collected from 153 patients (64 men, 89 women, mean age 53.9 ± 0.9 years), most of whom were malnourished. The measurements were made before and during a course of total parenteral nutrition. Measurements were also made on a group of morbidly obese patients at varying intervals following weight-reduction surgery. The nutritional state of these patients was determined by measuring the various components of body composition. A multiple-isotope dilution technique was used to determine the body composition.[8] The patients were injected with 500 μCi of tritiated water and 8 μCi of sodium 22. Blood samples were drawn before and at 4 and 24 hours after injection. Plasma tritium concentration at 24 hours corrected for urine loss was used to calculate the total body water (TBW). The plasma ^{22}Na activity, also corrected for urine loss, was used to calculate the exchangeable sodium (Na_e). An indirect method was used to calculate the total exchangeable potassium (K_e),[8] according to the following equation: $K_e = R(TBW) - Na_e$, where R is the ratio of the sum of sodium and potassium divided by the water content, as measured in an aliquot of whole blood.[8] This technique has been established experimentally in both animals and man.[8] To correct for body size, these data are expressed as a function of total body water, which is more accurate than body weight, since it is linearly related to the lean body mass and the resulting measurement is thus independent of the degree of adiposity. Additional measurements of body composition were obtained by the following calculations: LBM = TBW/0.73, BF = body weight - LBM, BCM = 0.00833 K_e and ECM = LBM - BCM, where LBM = lean body mass, BF = body fat, BCM = body cell mass and ECM = extracellular mass.

The total lymphocyte counts were determined either by manual counting of a Wright's smear or automated counting with a Coulter counter. The lymphocyte count was correlated with the nutritional state, as measured by the body composition parameters, by a standard linear regression.[9] All means are listed with the standard error of the mean. Differences

between the two sets of measurements, which were made twice in the same patient at different times, were analysed by the paired Student's *t*-test. A p value of less than 0.05 indicated a significant difference.

Results

The total lymphocyte count was correlated with the body cell mass (Fig. 1). The body cell mass is represented by the total exchangeable potassium divided by total body water to normalize for body size (K_e/TBW) which in 25 normal volunteers was 80.0 ± 1.0 mmol/L with 95% confidence limits of 69.9 to 90.1 mmol/L.[2] The study patients had a mean K_e/TBW of 64.4 ± 0.7 mmol/L (ranging from 39.0 to 89.8 mmol/L), indicating that a large proportion had a depleted body cell mass. The total lymphocyte count was 1.807 ± 0.66 × 10^9/L (normal range in our laboratory 1.5 to 3.0 × 10^9/L). The regression was significant ($p < 0.05$), but the regression coefficient of r = 0.12 was poor. Moreover, the data were very scattered, resulting in wide 95% confidence limits. Consequently, for a normal K_e/TBW of 80.0 mmol/L, regression indicated a lymphocyte count of from 0, abnormally low, to 4.26 × 10^9/L, abnormally high. In Fig. 2, the lymphocyte count is correlated with the Na_e to K_e ratio. In malnutrition, the extracellular mass expands as the body cell mass is depleted. Consequently, the Na_e to K_e ratio is a sensitive index of the nutritional state. In the 25 healthy volunteers, the mean ratio was 0.98 ± 0.02, with 95% confidence limits of 0.74 ± 1.22.[2] Malnutrition is thus defined as a Na_e to K_e ratio greater than 1.22. In this group of patients, the mean ratio was 1.45 ± 0.04, indicating that a large proportion of patients in our study were malnourished. The regression between the Na_e to K_e ratio and the lymphocyte count was not significant (r = -0.09). This lack of correlation was supported by the wide scatter of data about the regression line.

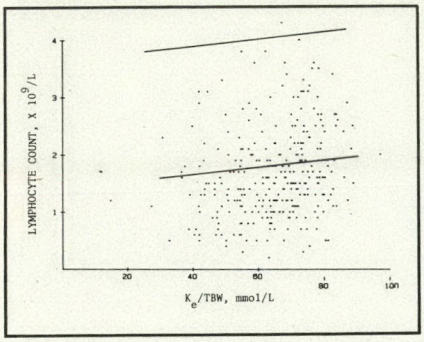


FIG. 1—Correlation between lymphocyte count and body cell mass (i.e., total exchangeable potassium/total body water [K_e/TBW]), 313 measurements. Correlation was significant ($p < 0.01$, r = 0.12); 95% confidence limits for correlation are included.

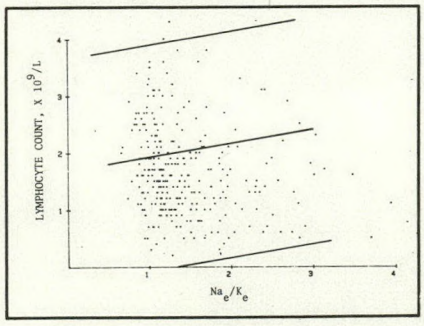


FIG. 2—Correlation between lymphocyte count and nutritional state measured by ratio of total exchangeable sodium to total exchangeable potassium (Na_e/K_e), 313 measurements. Correlation was not significant (r = -0.09); 95% confidence limits are included.

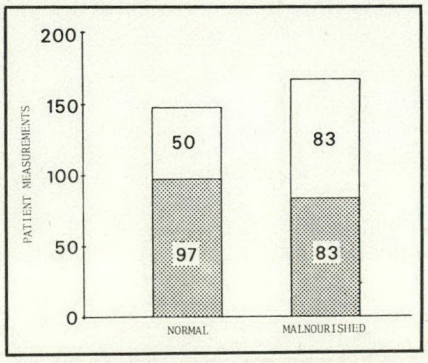


FIG. 3—One hundred and forty-seven measurements for patients who were nutritionally normal and 166 measurements for patients who were malnourished are represented in this histogram. Dotted area represents normal lymphocyte counts. Lymphocyte count in 50 of 147 measurements incorrectly indicated that normal patients were malnourished, for false-positive rate of 34%. Lymphocyte count incorrectly indicated in 83 of 166 measurements that malnourished patients were normal, for false-negative rate of 50%.

The patients were divided into those with a normal nutritional state and those with malnutrition based on their body composition (Fig. 3). The lymphocyte count correctly identified a normal nutritional state in 97 of 147 measurements (66%) but incorrectly indicated that malnourished patients were normal in 83 of 166 measurements, for a false-negative rate of 50%. Malnourished patients were correctly identified by the lymphocyte count in 83 measurements but in 50 measurements in which the patients had normal nutritional state, the measurement incorrectly identified the patients as malnourished, for a false-positive rate of 34% (50 of 147).

Seventy-eight patients with 97 pairs of measurements separated by a substantial time interval were divided into three groups based on the observed changes in their nutritional state (Table I). This permitted a comparison of changes in body composition, and thus the nutritional state, with changes in the lymphocyte count. There was nutritional improvement in 54 measurements. The body cell mass significantly ($p < 0.001$) increased from 15.4 ± 0.6 kg to 18.0 ± 0.8 kg, as reflected by the significant ($p < 0.001$) increase in K_e/TBW. This nutritional improvement was accompanied by a significant ($p < 0.01$) decrease in the extracellular mass and a significant ($p < 0.001$) decrease in the Na_e/TBW from 92.6 ± 1.0 mmol/L to 86.0 ± 1.1 mmol/L. The significant ($p < 0.001$) decrease in the Na_e to K_e ratio from 1.71 ± 0.06 to 1.39 ± 0.04 reflects the nutritional changes in body composition. The lymphocyte count increased from 1.6 ± 0.12 × 10^9/L to

Table I—Body Composition and Total Lymphocyte Count for 78 Patients With 97 Sequential Studies

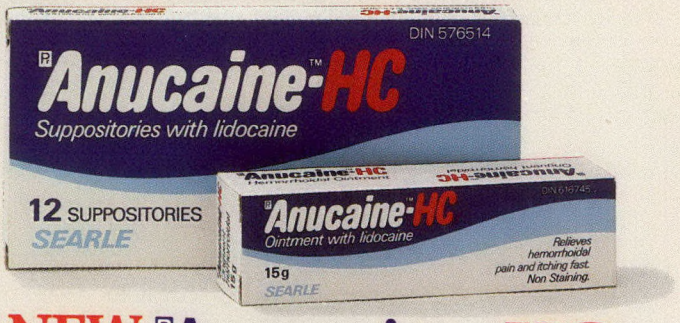
	Malnourished improved (n = 54)		Malnourished deteriorated (n = 28)		Normal deteriorated (n = 15)	
Measurement	M1	M2	M1	M2	M1	M2
Weight, kg	67.3 ± 3.0	68.1 ± 2.9	60.2 ± 3.4	62.4 ± 3.7	77.7 ± 9.4	73.7 ± 7.4
Body fat, kg	21.6 ± 2.1	22.2 ± 1.9	16.4 ± 3.5	16.1 ± 3.6	30.1 ± 6.2	28.5 ± 5.4
Lean body mass, kg	45.7 ± 1.7	45.9 ± 1.6	46.9 ± 2.2	49.3 ± 2.5	47.6 ± 3.7	45.2 ± 2.6
Body cell mass, kg	15.4 ± 0.6	18.0 ± 0.8*	16.5 ± 0.8	15.0 ± 0.7*	20.7 ± 2.1	16.3 ± 1.0*
Extracellular mass, kg	30.3 ± 1.3	27.9 ± 1.0*	30.3 ± 1.6	34.3 ± 2.1*	26.9 ± 1.7	28.9 ± 1.9*
Na_e/TBW, mmol/L	92.6 ± 1.0	86.0 ± 1.1*	90.9 ± 1.6	97.5 ± 1.7*	77.8 ± 1.0	87.8 ± 1.3*
K_e/TBW, mmol/L	55.8 ± 1.1	64.1 ± 1.3*	58.2 ± 1.4	51.2 ± 1.7*	70.2 ± 1.7	59.6 ± 1.7*
Na_e : K_e	1.71 ± 0.06	1.39 ± 0.04*	1.60 ± 0.07	2.00 ± 0.11*	1.12 ± 0.03	1.50 ± 0.07*
Total lymphocytes, X 10^9/L	1.60 ± 0.12	1.88 ± 0.17	1.99 ± 0.25	2.01 ± 0.19	1.60 ± 0.22	1.58 ± 0.18

M = measurement, Na_e = total exchangeable sodium, K_e = total exchangeable potassium, TBW = total body water.
*Significant difference ($p < 0.05$) from M1.

The thought foremost in the minds of hemorrhoid sufferers

Hemorrhoid sufferers want an end to the pain and itching; *fast* relief that *lasts*. ANUCAINE-HC can provide that relief.

ANUCAINE-HC contains lidocaine, a widely used local anesthetic, plus an astringent and hydrocortisone acetate. Also available without hydrocortisone as ANUCAINE.™ It is available in non-staining ointment and suppositories.



NEW Anucaine™-HC

the beginning of the end

SEARLE

Searle Pharmaceuticals
A Division of G.D. Searle & Co. of Canada, Limited
400 Iroquois Shore Road, Oakville, Ontario L6H 1M5

1.88 ± 0.17 × 10^9/L, but not significantly. Also, both the initial and final mean lymphocyte counts were within the normal range.

In the second group, 28 pairs of measurements were obtained from malnourished patients in which the nutritional state deteriorated. There was a significant ($p < 0.01$) decrease of the body cell mass with the mean K_e/TBW decreasing from 58.2 ± 1.4 mmol/L to 51.2 ± 1.7 mmol/L ($p < 0.001$). This was associated with a significant ($p < 0.01$) increase in the extracellular mass and the Na_e/TBW from 90.9 ± 1.6 mmol/L to 97.5 ± 1.7 mmol/L ($p < 0.001$). The mean Na_e to K_e ratio increased significantly ($p < 0.001$) from 1.60 ± 0.07 to 2.0 ± 0.11, indicating the deterioration. Again, the lymphocyte count did not change: both the initial lymphocyte count of 1.99 ± 0.25 × 10^9/L and the final mean of 2.01 ± 0.19 × 10^9/L were within the normal range.

In the last group of initially normal patients who subsequently became malnourished, there were 15 pairs of measurements. The deterioration was indicated by the significant ($p < 0.001$) increase in the Na_e to K_e ratio from a normal value of 1.12 ± 0.03 to a ratio of 1.50 ± 0.07. There was a significant ($p < 0.001$) decrease in the K_e/TBW and a significant ($p < 0.001$) increase in the Na_e/TBW. The lymphocyte count again remained basically unchanged with both the initial mean of 1.6 ± 0.22 × 10^9/L and the final mean of 1.58 ± 0.18 × 10^9/L being within normal limits.

Discussion

Malnutrition in hospitalized patients is not uncommon, but as nutritional support systems become more complex and more widely used, nutritional assessment must be accurate. This is important not only to identify the malnourished patient but also to follow the nutritional progress of these patients. Body composition measurements are an accurate assessment of the nutritional state.[10] Although precise, they are complex and difficult to perform. The total lymphocyte count is one of a number of readily available methods that are inexpensive and easy to measure. Reports have indicated that malnutrition can modify the immune response and thus alter measurements such as the total lymphocyte count.[3] In this study the lymphocyte count was evaluated as a nutritional parameter.

The total lymphocyte count did not correlate well with body cell mass. The correlation coefficient was poor and the scatter of the data was wide. Also, the total lymphocyte count had no correlation with the Na_e to K_e ratio, a sensitive index of nutritional state. This would indicate that the total lymphocyte count is not affected by malnutrition in these hospitalized patients. This indication was further supported by the sequential studies in which, despite significant changes in the nutritional state, the lymphocyte count did not change significantly. As a result of this poor association between the nutritional state and the total lymphocyte count, there was a false-positive rate of 34% and a false-negative rate of 50% when the lymphocyte count was used to detect malnutrition.

The results of this study indicate that the total lymphocyte is not affected by malnutrition. This does not mean that the immune response is not affected, since the total lymphocyte count is a poor measure of immunity. In previous studies of this type, the immune response was evaluated in terms of nutritional assessment of a population as well as the individual patient.[3] The lack of good correlation of the total lymphocyte count to the body composition, the wide confidence limits and the poor results of sequential studies indicate that the total lymphocyte count is of no value in assessing the nutritional state of an individual patient.

References

1. LAW DK, DUDRICK SJ, ABDOU NI: The effects of protein calorie malnutrition on immune competence of the surgical patient. *Surg Gynecol Obstet* 1974; 139: 257–66

2. SCRIMSHAW NS, TAYLOR CE, GORDON JE: *Interactions of Nutrition and Infection,* Monograph series 57, World Health Organization, Geneva, 1968

3. FORSE RA, CHRISTOU N, MEAKINS JL, MACLEAN LD, SHIZGAL HM: Reliability of skin testing as a measure of nutritional state. *Arch Surg* 1981; 116: 1284–8

4. BISTRIAN BR, BLACKBURN GL, SCRIMSHAW NS, FLATT JP: Cellular immunity in semistarved states in hospitalized adults. *Am J Clin Nutr* 1975; 28: 1148–55

5. DIONIGI R, ARISZONT A, DOMINIONI L, GNES F, BALLABIO A: The effects of total parenteral nutrition on immunodepression due to malnutrition. *Ann Surg* 1977; 185: 467–74

6. YOUNG GA, HILL GL: Assessment of protein-calorie malnutrition in surgical patients from plasma proteins and anthropometric measurements. *Am J Clin Nutr* 1978; 31: 429–35

7. BLACKBURN GL, BISTRIAN BR, MAINI BS, SCHLAMM HT, SMITH MF: Nutritional and metabolic assessment of the hospitalized patient. *JPEN* 1977; 1: 11–22

8. SHIZGAL HM, SPANIER AH, HUMES J, WOOD CD: Indirect measurement of total exchangeable potassium. *Am J Physiol* 1977; 233: F253–9

9. ARMITAGE P: *Statistical Methods in Medical Research,* Wiley, New York, 1971

10. FORSE RA, SHIZGAL HM: The Na_e/K_e ratio: a predictor of malnutrition. *Surg Forum* 1980; 31: 89–92

SHERIF S. HANNA, MD, FACS, FRCSC; YOGESH MAHESHWARI, MD; A.W. HARRISON, MD, FRCSC; G.A. TAYLOR, MD, FRCSC; H.A.B. MILLER, MD, FRCSC; R. MAGGISANO, MD, FRCSC

Blunt Liver Trauma at the Sunnybrook Regional Trauma Unit

Between June 1, 1976 and Mar. 31, 1983, the Sunnybrook Medical Centre Regional Trauma Unit in Toronto, Ont., admitted 145 patients with liver trauma; of these, 141 (97%) had sustained blunt liver trauma. Of 113 patients who underwent open peritoneal lavage, 112 had a true-positive lavage.

Resuscitation was successful in 137 patients and 134 of these underwent laparotomy. Seventy-nine (59%) of the 134 patients required only minor surgical treatment; the other 55 (41%) required major surgical procedures.

The overall mortality was 32% (47 of 145). Eight patients died during resuscitation but only one of them died of liver hemorrhage. Of the 39 patients who died after admission, the cause of death was head injury in 22, while 6 died of liver hemorrhage and 11 of other causes. Overall, liver hemorrhage was the cause of death in 15% of cases (7 of 47).

Entre le 1er juin 1976 et le 31 mars 1983, 145 patients victimes de traumatismes hépatiques sont entrés à l'Unité régionale de soins pour traumatisés du Sunnybrook Medical Centre à Toronto. Parmi ceux-ci, 141 (97%) avaient subi des contusions hépatiques. Sur 113 patients chez qui on pratiqua un lavage péritonéal, 112 eurent un résultat positif certain.

Cent trente-sept patients furent réanimés et 134 subirent une laparotomie. De ce dernier groupe, 79 (59%) ne nécessitèrent qu'une chirurgie mineure alors que les 55 (41%) autres devaient subir une intervention chirurgicale majeure.

La mortalité globale fut de 32% (47 sur 145). Huit patients sont décédés pendant les tentatives de réanimation mais un seul d'entre-eux est mort d'hémorragie hépatique. Des 39 patients qui sont décédés après leur hospitalisation, 22 sont décédés des suites d'un traumatisme crânien, 6 d'hémorragie hépatique et 11 d'autres causes. Dans l'ensemble, l'hémorragie hépatique fut la cause de décès dans 15% des cas (7 sur 47).

Motor vehicle accidents are the major cause of blunt abdominal trauma in Canada and, as such, constitute a serious health-care problem.[1] After the spleen, the liver is the most commonly injured organ and is associated with multiple organ injuries in about 50% of patients.[2,3] Although the prognosis for these critically injured patients has improved markedly, considerable disagreement still exists among experienced trauma surgeons as to the preferred method of management after blunt hepatic injury.

The purpose of this communication is to review our experience with liver trauma at Sunnybrook Medical Centre Regional Trauma Unit, with emphasis on blunt trauma, in order to evaluate current methods of diagnosis and treatment, and the complications and mortality of hepatic trauma. We are the major trauma centre for southern Ontario, with 85% of our patients being referred from other institutions.

Methods

The charts of all patients with liver injuries admitted between June 1, 1976 and Mar. 31, 1983 were reviewed to determine age, sex, length of hospital stay, type of trauma, diagnosis, type of liver injury, treatment, complications, associated injuries, injury severity scores and cause of death.

Patients with liver injuries who could not be successfully resuscitated and died in the emergency room were included. All patients who were treated elsewhere for liver injury but were transferred to Sunnybrook Medical Centre for postoperative care or care of associated injuries were excluded.

Open peritoneal lavage was considered positive when the fluid was either grossly bloody or the erythrocyte count was greater than 10.0×10^9/L.* All patients with a positive peritoneal lavage were operated upon to treat the intra-abdominal hemorrhage. Liver-related mortality was calculated by reviewing the cause of death. An abbreviated injury severity score (ISS 1980 version) for each patient was calculated according to the rules of the American Association for Automotive Medicine.[4] Injury severity scores were compared by Student's *t*-test.

Findings

During the study period, Sunnybrook Medical Centre Regional Trauma Unit admitted 1173 trauma patients. Of these, 145 (101 males, 44 females) had sustained liver trauma; 141 (97%) had blunt injury, while 4 (3%) had sustained a penetrating stab injury.

Cause of Injury

Motor vehicle accidents were the cause of injury in 127 (90%) of those with blunt trauma. The other causes of blunt trauma were accidental or suicidal falls, a kick by a horse and a crush injury in a ferris wheel. Of the 145 patients with liver trauma, 79 (54%) were between 10 and 30 years old.

Lavage

Open peritoneal lavage was done in 113 patients, with a true-positive lavage in 112; 1 patient had a false-negative result. This patient had signs of peritoneal injury

From the Department of Surgery, Division of General Surgery, Sunnybrook Medical Centre and University of Toronto, Toronto, Ont.

Presented at the 7th annual meeting of the Canadian Association of General Surgeons, Montreal, PQ, Sept. 12, 1984, held in conjunction with the 53rd annual meeting of the Royal College of Physicians and Surgeons of Canada

Accepted for publication Feb. 4, 1985

Reprint requests to: Dr. S.S. Hanna, Department of Surgery, Rm. 1A-1034, Sunnybrook Hospital, 2075 Bayview Ave., Toronto, Ont. M4N 3M5

*Currently, only lavage counts greater than 20.0×10^9/L erythrocytes are considered positive.

2 days after admission and the liver injury was discovered at operation.

Diagnosis and Treatment

Of the 145 patients with liver trauma who were brought to the emergency room, 137 were successfully resuscitated. Laparotomy was done in 134 of these, while 3 patients in whom a diagnosis of subcapsular hematoma was made clinically were treated conservatively. The latter did well on follow-up. Sixteen of the 134 patients required immediate laparotomy for obvious intra-abdominal injuries (4 patients had penetrating injuries). Two had laparotomy after laparoscopy. Three others with liver injuries who had laparotomy had incomplete records as to how the diagnosis of intraperitoneal bleeding was made.

Ninety-six (74%) of 130 patients who underwent laparotomy were found to be bleeding from their liver injury at operation, whereas in 34 (26%) the bleeding had already stopped. The records did not elaborate on this point in the other four patients. Liver injury was limited to the right lobe in 65 patients (54%), to the left lobe in 35 (29%), both lobes were injured in 19 patients (16%) and 1 patient (0.8%) had injury limited to the portal vein which was bleeding profusely. This was repaired and the patient did well. The location of injury was not noted in the other 14.

In 22 (16%) patients whose bleeding was found to have ceased when laparotomy was done, no definitive treatment was necessary. Minor surgical treatment, which consisted of peritoneal drainage or use of hemostatic agents, or both, was necessary in 57 patients (43%) (Table I). Of 55 patients who needed major intervention, the liver wound was sutured and drained in 36. In 12 patients, the liver was only sutured. The other seven patients required resectional débridement.

Deaths

The mortality for the series of 145 patients with liver injury was 32% (47 patients). Eight died during resuscitation but in only one was death due to liver hemorrhage (Table II). Of the 39 patients who died after admission, head injury was the cause in 22 and various other causes in 11 (Table III). Six patients died of liver hemorrhage (Table IV). Overall, therefore, hepatic bleeding was the cause of death in 7 of the 47 patients (15%). The other 40 patients died of various other causes, mostly head injuries (24 patients). The mean ISS for the 98 survivors was 40 ± 11 (standard deviation) which differed significantly ($p < 0.0005$) from that for the 47 nonsurvivors, 57 ± 12.

There were 45 complications in 29 of the 98 surviving patients (Table V). However, only five patients required reoperation, two for subphrenic abscess, one for a pancreatic pseudocyst, one for gallbladder necrosis and one for abdominal wall bleeding. All these patients did well after reoperation.

Table I—Surgical Treatment

Type of treatment	No. of patients (%)
No treatment	22 (16)
Minor surgical treatment	
Drainage only	13 (10)
Hemostatic agents only	20 (15)
Hemostatic agents and drainage	24 (18)
Major surgical treatment	
Suture and drainage	36 (27)
Suture only	12 (9)
Resectional débridement	7 (5)
Totals	134 (100)

Table II—Causes of Death in Eight Patients Who Died During Resuscitation

Cause	No. of patients
Severe cardiopulmonary injuries	3
Head injury	2
Aortic – inferior vena caval tears	2
Liver hemorrhage	1

Table III—Miscellaneous Causes of Death After Admission in 11 Patients

Cause	No. of patients
Shock from nonhepatic causes	3
Expanding retroperitoneal hematoma	2
Lung injury and respiratory failure	2
Myocardial contusion	2
Pulmonary embolism	1
Ruptured thoracic aorta	1

Discussion

At Sunnybrook Medical Centre Regional Trauma Unit, 12% (145) of our 1173 trauma patients suffered a liver injury; 97% a blunt liver injury and 3% a penetrating stab wound. There were no gunshot wounds to the liver. These figures, although similar to those reported from the United Kingdom,[5] Sweden[6] and Malaysia,[7] are in sharp contrast to the figures reported from the United States,[8-16] where penetrating injuries form the majority of traumatic injuries to the liver. The finding that 54% of our patients were between 10 and 30 years of age compares closely with other reported series.[17-20]

Often the diagnosis of hepatic injury is not made until laparotomy is performed, since the signs of liver injury, which include shock, contusion over lower chest and upper abdomen, shoulder-tip pain and positive peritoneal lavage, are all nonspecific. Open peritoneal lavage is extremely useful in the diagnosis of intra-abdominal bleeding. We had true-positive findings in 112 of 113 patients in whom open peritoneal lavage was performed. Moon and Federle[21] suggested that computerized tomography combines the best features of all available diagnostic techniques in evaluating the patient with hepatic injury. It is rapid, noninvasive, accurately defines the extent of hepatic or other abdominal injuries and quantifies the size of associated hemoperitoneum. We have recently begun a study using this technique in the diagnosis of blunt abdominal trauma.

The incidence of subcapsular hematoma following blunt abdominal trauma has been reported to range from 0.33% to 12% of all liver trauma. Conservative treatment of subcapsular hematoma is favoured by some,[2,22,23] while others caution against it for the fear of delayed rupture, infection or hemobilia.[10] Our three patients with subcapsular hematoma were treated conservatively and all did well.

The surgical treatment of a patient with hepatic trauma depends on the type of wound encountered at operation.[24] Some minor lacerations that have stopped bleeding may not require repair, but it is impossible to select preoperatively patients with minor injuries that will stop

Table IV—Surgical Procedures and Complications in Six Patients Who Died of Liver Hemorrhage After Laparotomy

First procedure	Complication	Second procedure	Injury severity score
Suture and drainage	Rebleeding and disseminated intravascular coagulation	Suture and drainage	59
Suture and drainage	Rebleeding and disseminated intravascular coagulation	None	66
Resectional débridement	Continued shock	None	59
Resectional débridement	Rebleeding and disseminated intravascular coagulation	Resectional débridement	59
Packing elsewhere	Rebleeding and disseminated intravascular coagulation	Resectional débridement at Sunnybrook	33
Packing elsewhere	Cirrhotic liver	Suture and drainage at Sunnybrook	34

bleeding. Use of hemostatic agents like Avitene, Surgicel, Oxycel, liquid thrombin or packing were sufficient to control bleeding in patients with minor injuries. Of the patients who required major surgical treatment, sutures had to be applied to the liver in 87% and resectional débridement was needed in 13%. Initial management of severe lacerations is aided by digital or atraumatic clamp compression of the hepatoduodenal ligament as described by Pringle in 1908.[25] This will permit ligation of small vessels and débridement.[24]

The role of hepatic artery ligation in controlling hemorrhage has frequently been supported[18,22,26,27] and disputed.[9,10] Walt[9] has suggested that we may be trading short-term gains in hemostasis for long-term hepatic sepsis with delayed mortality. We did not use hepatic artery ligation in any of our patients; we believe that although this method is occasionally useful, it is overused.

The rate of hepatic resectional débridement, which consists of limited resection of devitalized tissue along the lines of injury, has declined progressively from a high of 46%[7] to as low as 3%.[28] It was used in 5% of our patients who underwent laparotomy for hepatic trauma. This rate compares well with those of other series.

After bleeding has been controlled and the wound debrided, adequate drainage should be provided. Few communications have questioned the value of peritoneal drainage,[29,30] which was used in 60% of our patients who underwent laparotomy.

Merendino and colleagues[31] recommended drainage of the common bile duct using a T tube in severe liver trauma to decrease likelihood of biliary fistulas. Lucas and Ledgerwood[32] have shown a striking increase in morbidity following T-tube drainage, and we agree that it should not be used.

Shotgun wounds are the most lethal liver injuries, followed in descending order by blunt trauma and gunshot and stab wounds.[6,9] Isolated hepatic injury occurs in less than 10% of patients with blunt trauma and is associated with a mortality of 5% which increases to over 55% when six or more organs are involved.[13,14] Our overall mortality was 32% (47 of 145). True liver-related mortality due to hemorrhage was seen in 15% (7 of 47) of those who died. This was mostly due to the development of profound coagulopathy associated with long-standing shock that did not respond to correction of blood volume and clotting factors.[11,22] The other 40 who died could be divided into two main groups: those who died of severe head injuries either before or after resuscitation (24 patients) and those who died of miscellaneous causes (16 patients). Our figures compare well with blunt trauma mortality in other series (Table VI).[5-9,12-16,18-20,28,29,33,34] At Sunnybrook Medical Centre, approximately 70% of patients admitted with multiple injuries have a serious head injury, which is an important cause of morbidity and death.[35] In view of the severe type of blunt hepatic trauma at our centre, it is not surprising that our overall mortality is higher than that of some reported series in which penetrating liver injury dominates and carries a mortality of less than 5%.

Table V—Complications in the 98 Surviving Patients (n = 29)

Complication	No. of episodes
Sepsis	10*
Liver failure	6
Disseminated intravascular coagulation	6
Biliary fistula	4
Renal failure	4
Pulmonary embolism	4
Other	11

*Includes 3 subphrenic abscesses.

Table VI—Mortality for Blunt Liver Trauma Reported in Literature

Authors	Location of study	Total no. of patients	No. of patients with blunt trauma	Mortality, %	
				Overall	Blunt trauma
Schrock and associates, 1968[8]	San Francisco	61	20	24	65
Walt, 1969,[12] 1978[9]	Detroit	436	50	11	30
Walt, 1978[9]	Detroit	637	57	15	–
		331	40	12	20
Balasegaram, 1976[7]	Malaysia	179	90 (MVA 71)	17	14
Defore and associates, 1976[13]	Houston	1590	240	13	30
Levin and associates, 1978[14]	New Orleans	546	76 (MVA 75%)	10	28
Fischer and associates, 1978[29]	Minnesota	303	–	22	29
Elerding and associates, 1979,[15] 1980[20]	Denver	225	66	15	20
Aldrete and associates, 1979[16]	Alabama	108	48	17	–
Pachter and Spencer, 1979[28]	New York	85	8	7	–
Miller and Bernstein, 1980[18]	Irving (Calif)	56	34	9	–
Hasselgren and associates, 1981[6]	Sweden	58	20 (MVA 9)	19	30
Calne and associates, 1982[5]	Cambridge (UK)	26	25 (MVA 25)	15	–
Thomas, 1983[34]	Hamilton	82	–	17	–
Corica and Powers, 1975[33]	Albany	?	75	–	33
Witte and Zokoski, 1983[19]	Arizona	?	26	–	8
Current series	Toronto	145	141 (MVA 127)	32	32

MVA = motor vehicle accident.

Conclusions

Most blunt hepatic trauma can be managed adequately using a simple conservative approach, based on well-established principles. Early diagnosis, prompt hemostasis, restoration of blood volume and coagulation, prevention of hypothermia, hypotension and acidosis and treatment of associated injuries are crucial in saving the patient. Surgical principles of management include direct control of hemorrhage, débridement of devitalized liver tissue and adequate drainage.

References

1. BURNS CM: Symposium on trauma for the general surgeon. 1. An accident health care program: the organization and development of regional trauma units. *Can J Surg* 1978; 21: 507–9
2. CHEATHAM JE JR, SMITH EI, TUNELL WP, ELKINS RC: Nonoperative management of subcapsular hematomas of the liver. *Am J Surg* 1980; 140: 852–7
3. ALI J: Symposium on trauma for the general surgeon. 3. Abdominal trauma with special reference to hepatic trauma. *Can J Surg* 1978; 21: 512–6
4. Committee on Injury Scaling: *The Abbreviated Injury Scale, 1980 Revision,* American Association of Automotive Medicine, Morton Grove, Ill., 1980
5. CALNE RY, WELLS FC, FORTY J: Twenty-six cases of liver trauma. *Br J Surg* 1982; 69: 365–8
6. HASSELGREN PO, ALMERSJÖ O, GUSTAVSSON B, SEEMAN T: Trauma to the liver during a ten-year period. With special reference to morbidity and mortality after blunt trauma and stab wounds. *Acta Chir Scand* 1981; 147: 387–93
7. BALASEGARAM M: The surgical management of hepatic trauma. *J Trauma* 1976; 16: 141–8
8. SCHROCK T, BLAISDELL FW, MATHEWSON C JR: Management of blunt trauma to the liver and hepatic veins. *Arch Surg (Chicago)* 1968; 96: 698–704
9. WALT AJ: Founder's lecture: the mythology of hepatic trauma — or Babel revisited. *Am J Surg* 1978; 135: 12–8
10. LUCAS CE, LEDGERWOOD AM: Prospective evaluation of hemostatic techniques for liver injuries. *J Trauma* 1976; 16: 442–51
11. LUCAS CE, WALT AJ: Critical decisions in liver trauma. Experience based on 604 cases. *Arch Surg* 1970; 101: 277–83
12. WALT AJ: The surgical management of hepatic trauma and its complications. *Ann R Coll Surg Engl* 1969; 45: 319–39
13. DEFORE WW JR, MATTOX KL, JORDAN GL JR, BEALL AC JR: Management of 1,590 consecutive cases of liver trauma. *Arch Surg* 1976; 111: 493–7
14. LEVIN A, GOVER P, NANCE FC: Surgical restraint in the management of hepatic injury: a review of Charity Hospital experience. *J Trauma* 1978; 18: 399–404
15. ELERDING SC, ARAGON GE, MOORE EE: Fatal hepatic hemorrhage after trauma. *Am J Surg* 1979; 138: 883–8
16. ALDRETE JS, HALPERN NB, WARD S, WRIGHT JO: Factors determining the mortality and morbidity in hepatic injuries. Analysis of 108 cases. *Ann Surg* 1979; 189: 466–74
17. BLUETT MK, WOLTERING E, ADKINS RB: Management of penetrating hepatic injury. A review of 102 consecutive patients. *Am Surg* 1984; 50: 132–42

18. MILLER DR, BERNSTEIN JM: Hepatic trauma. A review of 56 consecutively treated patients. *Arch Surg* 1980; 115: 175–8
19. WITTE CL, ZUKOSKI CF: A rational approach to serious blunt hepatic injury. *Am Surg* 1983; 49: 446–53
20. ELERDING SC, MOORE EE JR: Recent experience with trauma of the liver. *Surg Gynecol Obstet* 1980; 150: 853–5
21. MOON KL JR, FEDERLE MP: Computed tomography in hepatic trauma. *AJR* 1983; 141: 309–14
22. DUNHAM CM, MILITELLO P: Surgical management of liver trauma. *Am Surg* 1982; 48: 435–9
23. ATHEY GN, RAHMAN SU: Hepatic haematoma following blunt injury: non-operative management. *Injury* 1982; 13: 302–6
24. HANNA SS, JIRSCH DW: Management of hepatic injury. *Can Med Assoc J* 1977; 117: 352–3
25. PRINGLE JH: Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg* 1908; 48: 541–9
26. MAYS ET: The hazards of suturing certain wounds of the liver. *Surg Gynecol Obstet* 1976; 143: 201-4
27. Idem: Hepatic trauma. *N Engl J Med* 1973; 288: 402–5
28. PACHTER HL, SPENCER FC: Recent concepts in the treatment of hepatic trauma: facts and fallacies. *Ann Surg* 1979; 190: 423-9
29. FISCHER RP, O'FARRELL KA, PERRY JF: The value of peritoneal drains in the treatment of liver injuries. *J Trauma* 1978; 18: 393–8
30. CERISE EJ, PIERCE WA, DIAMOND DL: Abdominal drains. Their role as source of infection following splenectomy. *Ann Surg* 1970; 171: 764
31. MERENDINO KA, DILLARD DH, CAMMOCK EE: The concept of surgical biliary decompression in the management of liver trauma. *Surg Gynecol Obstet* 1963; 117: 285–93
32. LUCAS CE, LEDGERWOOD AM: Controlled biliary drainage for large injuries of the liver. *Surg Gynecol Obstet* 1973; 137: 585–9
33. CORICA A, POWERS SR JR: Blunt liver trauma: an analysis of 75 treated patients. *J Trauma* 1975; 15: 751–6
34. THOMAS EJ: Symposium on trauma. 4. Major liver trauma. *Can J Surg* 1983; 26: 27–30
35. SCHWARTZ ML: Symposium on trauma. 3. Head injury in multiple trauma. Ibid: 23–6

SESAP IV Critique

ITEM 118

In the management of severe hepatic injuries, enthusiasm for resection has been replaced by the belief that persistence in local hemostasis and débridement will control most hepatic bleeding. Routine T-tube drainage of the common duct has been shown to be both unnecessary and detrimental for these patients, most of whom have ducts of normal size. If T-tube drainage is used, postoperative sepsis and gastrointestinal bleeding are increased.

Major liver injury is associated with a mortality in excess of 15%. Bleeding from liver parenchyma in some instances can arise from branches of the hepatic artery. With local hemostatic measures, ligation of the hepatic artery should only rarely be required for the management of major liver injuries. If used, however, ligation has been shown to be safe, with no significant long-term effect on liver function.

C

Reference

118/1. Walt AJ: The mythology of hepatic trauma — or Babel revisited. Am J Surg 135: 12-18, 1978

How do you get a balanced meal through a tube?

isocal*

An excellent choice

To provide a tube-fed patient with a nutritionally balanced diet that is isotonic, lactose-free, has a readily absorbed fat blend and appropriate vitamin and mineral levels, make certain they receive ready-to-feed ISOCAL.

ISOCAL
Complete nutritional value
Problem-free formulation

Mead Johnson CANADA

*T.M. Auth. User

Symposium on Outpatient Anorectal Procedures

EUGENE P. SALVATI, MD, FACS

1. Pilonidal Disease

Many procedures have been advocated to treat pilonidal disease, suggesting that no one method is highly efficacious. In the office, the surgical approach is directed towards three aspects of the condition: pilonidal abscess, recurrent pilonidal disease following surgery and chronic pilonidal disease following spontaneous rupture of an abscess or secondary to incision and drainage.

In managing the acute pilonidal abscess, an intradermal injection is given over the indurated, fluctuant area as well as the midline orifice which can almost always be identified. The midline orifice is incised and the incision carried into the abscess cavity. The edges of the cavity are excised. Healing takes place secondarily. A second procedure is rarely needed.

Plusieurs opérations ont été proposées pour traiter le kyste pilonidal, ce qui laisse supposer qu'aucune n'est très efficace. Dans le cabinet de consultation, la chirurgie s'attaque à trois aspects de cette affection: l'abcès pilonidal, la récidive post-chirurgicale du kyste pilonidal et le kyste pilonidal chronique consécutif à la rupture d'un abcès ou secondaire à une incision avec drainage.

Devant un abcès pilonidal aigu, on administre une injection intradermale au-dessus de la zone indurée mobile de même que de l'orifice médian, lequel peut presque toujours être identifié. Une incision est pratiquée par l'orifice médian jusque dans l'abcès. Les bords de la cavité sont excisés. La guérison se fait par seconde intention. Une deuxième opération est rarement nécessaire.

Pilonidal disease has posed a problem in surgical management since Anderson[1] in 1847 first described marsupialization of the tract for cure. The etiology of the disease remains obscure. It does not occur before puberty and is rare in black people and in Asiatics. It is far more common among hirsute individuals[2] and there is a definite association with trauma. During World War II, soldiers lost many man hours due to "jeep disease".[3] The combination of poor personal hygiene due to battlefield conditions and the trauma of riding the hard seats of jeeps over difficult terrain were the main causative factors. The presence of the midline pits very evenly placed over the postsacral area suggests a congenital origin.[4] With the development of secondary sexual characteristics at puberty, the hair becomes more profuse and coarse. Shafts of exfoliated hair, particularly from the scalp, then penetrate the pits or theoretically can themselves cause pits and, with poor personal hygiene and trauma, a secondary infection develops. Pathologically, hair follicles have never been found in the sinus tracts, proving that the hair is extraneous to the area. Moreover, frequently no connection between adjacent midline orifices can be seen.

Treatment

Many procedures have been advocated to treat pilonidal disease, which suggests that no one method is highly efficacious. Sebrechts[5] in his bibliography of pilonidal disease listed 936 separate papers, the majority of which described its management. Excision and primary closure,[6] marsupialization,[7] split-thickness grafts,[8] Z-plasty,[9] injection of sclerosing solutions,[10] excision and delayed closure,[11] electrocoagulation,[12] semiprimary closure,[13] gluteal fascioplasty[14] and incision and curettage[15] have all been advocated. The management of this condition in the office has been suggested before and therefore is not new.[16-18] The office surgical approach revolves around three aspects of the condition: pilonidal abscess, recurrent pilonidal disease following surgery and chronic pilonidal disease following spontaneous rupture of an abscess or secondary to previous incision and drainage.

Acute Pilonidal Abscess

The acute pilonidal abscess presents as a painful swelling in the postsacral area cephalad to the coccyx and generally presenting to the right or the left of the midline. Induration or fluctuation, or both, can be seen and palpated and nearly always a midline orifice can be identified. The skin overlying the abscess cavity is injected with 1 to 2 mL of a solution of 0.25% bupivacaine with 1:200 000 epinephrine, using a 30-gauge dental needle. It is important to inject the anesthetic solution intradermally to achieve adequate anesthesia. The skin will blanch if the injection is being given intradermally. Injection into the abscess cavity should be avoided since it will be painful and anesthesia will be inadequate due to the acid pH. A small probe is then inserted through the midline orifice into the abscess cavity. This midline pit can usually be identified. The incision is extended from the midline orifice the full length of the abscess cavity. The edges of the abscess cavity are excised to expose the posterior wall completely. It may be necessary to inject further local anesthetic into the skin edges to accomplish this. If a midline orifice cannot be identified, the incision should still be made through the

From the Department of Surgery, Rutgers Medical School, Plainfield, NJ

Presented as part of a symposium on outpatient anorectal procedures by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, Calgary, Alta., Sept. 21, 1983

Accepted for publication Nov. 19, 1984

Reprint requests to: Dr. Eugene P. Salvati, 1010 Park Ave., Plainfield, NJ 07060, USA

midline and then extended into the abscess cavity. The posterior wall of the abscess is not incised and the granulation tissue is either cauterized with a silver nitrate stick or curetted out. A gauze dressing is placed into the wound, then cotton and a V pad that is taped into place. The patient should not remove the dressing until the following day since that may result in bleeding. Hot tub baths are started the following day and continued until the wound is healed. The healing time is generally 2 weeks and the patient experiences minimal discomfort. Recurrence of the pilonidal cyst managed in this way is unusual; thus, the treatment is definitive.

Recurrent Pilonidal Disease

Management of a recurrent pilonidal sinus after formal surgery can be adapted to office surgery. The recurrence in most cases develops in the caudal portion of the scar. A blind cavity or sinus tract is frequently encountered through a midline opening. A local anesthetic is administered and an incision made directly over the probe, exposing the sinus tract or cavity. The posterior wall of the tract is left intact but is scraped free of granulation tissue and the edges of the tract are debrided. Frequently, the posterior wall is completely epithelialized and leaving it intact shortens the healing period. A dressing is applied as described and hot baths are begun the following day. If the wound is large, the patient is urged to use a Water Pik once daily to keep the wound clean as recommended by Hoexter.[19] The patient is seen at weekly intervals when the hair is shaved back from the skin edges of the wound, the granulation tissue removed and the wound cauterized with 10% silver nitrate. The healing time averages 3 to 4 weeks, depending on the size of the wound.

Chronic Pilonidal Disease

The chronically draining pilonidal cyst that develops after incision and drainage of an abscess or spontaneous rupture of a pilonidal abscess, can again, in most instances, be managed in the office. The anesthetic injection, however, is slightly different. To a 50-mL vial of 0.25% bupivacaine with 1:200 000 epinephrine, 2 mL of hyaluronidase (300 turbidity reducing units) are added. The hyaluronidase breaks down the intracellular cement and brings about rapid diffusion of the solution with immediate anesthesia. The hair about the cyst is first shaved and then the anesthetic is administered, placing the solution circumferentially about the cyst as well as deep to the cyst between the cyst and the postsacral fascia. With a no. 15 blade disposable scalpel, a midline incision is made through all midline orifices, exposing the cyst or sinus tract. The edges of the wound are cut back and bevelled. The posterior wall of the cyst is left intact, but all granulation tissue is vigorously removed. Hemostasis is secured by electrocautery. A piece of Surgicel followed by cotton and several V pads are then applied. The dressing is removed the following day and hot baths are started. Following each hot bath, a 4 × 4-inch gauze soaked in 0.5% silver nitrate solution is applied to the wound followed by a dry gauze pad to hold it in place. The use of the silver nitrate solution keeps the wound clean and the granulation tissue down, thus speeding up the healing process. In the nervous, apprehensive patient, this same procedure is carried out in the hospital in a similar manner but with the addition of diazepam intravenously in increments of 2.5 mg up to 10 to 15 mg. The patient is seen at weekly intervals and is instructed to use a Water Pik if the wounds are not clean. The hair is always shaved back from the wound edges at these weekly visits. In a personal review[20] of 126 patients treated in this manner in the hospital for pilonidal disease, the recurrence rate was 20.9% and the average healing time was less than 2 months. The recurrences were treated by office procedures in all but one instance.

Discussion

I agree with Hurst[21] that pilonidal disease is overtreated. Wide, radical excision down to the postsacral fascia under a major anesthetic leaving a wound that may take 3 to 6 months to heal has no place in the management of pilonidal disease. The high recurrence rate appears to be due to the development of new disease rather than recurrence of the old since it is difficult to believe that the surgeon leaves any cysts or sinus tracts behind. When healing time is prolonged and the wound is not kept meticulously clean and free of hair, new sinus tracts and cysts may be formed by the inclusion of hair deep in the wound with epithelialization over the enclosed hair. The object should be to create as small a wound as possible and get it healed as quickly as possible. Cleanliness is the hallmark of success in the proper management of pilonidal disease.

References

1. ANDERSON AW: Hair extracted from an ulcer. *Boston Med Surg J* 1847; 36: 74
2. GIFFORD H: Role of hair in pathogenesis of postanal pilonidal sinus. *Stanford Med Bull* 1954; 12; 185–9
3. BUIE LA: Jeep disease (pilonidal disease of mechanized warfare). *South Med J* 1944; 37: 103–9
4. HAWORTH JC, ZACHARY RB: Congenital dermal sinuses in children; their relation to pilonidal sinuses. *Lancet* 1955; 2: 10–4
5. SEBRECHTS P: *Pilonidal Disease (Bibliography)*, Naval Regional Medical Center, San Diego, Calif., Tab 1
6. CASTEN DF, TAN BY, AYUYAO A: A technique of radical excision of pilonidal disease with primary closure. *Surgery* 1973; 73: 109–14
7. FREUND SJ, REDDING MD: Marsupialization; surgical procedure for eradication of pilonidal cyst and sinuses. *Am J Surg* 1948; 76: 286–8
8. BORDE CM, BRUCK HG: [Indications for split thickness skin grafting in recurrent pilonidal sinus.] *Wien Klin Wochenschr* 1973; 85: 624–8
9. LAMKE LO, LARSSON J, NYLÉN B: Treatment of pilonidal sinus by radical excision and reconstruction by rotation flap surgery of Z-plasty technique. *Scand J Plast Reconstr Surg* 1979; 13: 351–3
10. KNOWLTON DJ: Pilonidal cyst; report of 6 cases and comment on treatment by injection. *Conn Med J* 1945; 9: 28–9
11. ABRAMSON DJ: Excision and delayed closure of pilonidal sinuses. *Surg Gynecol Obstet* 1977; 144: 205–7
12. JACOBSON P: Electrocoagulation of congenital sinuses, with special reference to pilonidal sinus. *South Med J* 1947; 40: 980–9
13. ABRAMSON DJ: Outpatient management of pilonidal sinuses: excision and semiprimary closure technic. *Milit Med* 1978; 143: 753–7
14. DWIGHT RW: Pilonidal sinus; evaluation of plastic closure using flaps of gluteal muscle. *AMA Arch Surg* 1952; 64: 438–42
15. DA SILVA JH: [Surgical treatment of pilonidal cyst by incision and curettage.] *Rev Hosp Clin Fac Med Sao Paulo* 1974; 29: 199–203
16. CRILE G JR: Definitive ambulatory treatment for infected pilonidal cysts. *Surgery* 1948; 24: 677–9
17. HURST DW: The evolution of management of pilonidal sinus disease. *Can J Surg* 1984; 27: 603–5
18. MUELLER CB: Excision of pilonidal sinus as an office procedure (E). Ibid: 526
19. HOEXTER B: Use of Water Pik lavage in pilonidal wound care. *Dis Colon Rectum* 1976; 19: 470–1
20. WEINSTEIN MA, RUBIN RJ, SALVATI EP: The dilemma of pilonidal disease: pilonidal cystotomy, reappraisal of an old technique. *Dis Colon Rectum* 1977; 20: 287–9
21. HURST DW: Pilonidal sinus: an overtreated disease (E). *Can J Surg* 1971; 14: 98–9

BOOKS RECEIVED

continued from page 211

The Hereditary Ataxias and Related Disorders. Clinical Neurology and Neurosurgery Monographs, vol. 6. A.E. Harding. 268 pp. Illust. Academic Press Canada, Don Mills, Ont., 1984. $78.40. ISBN 0-443-02599-1.

Maingot's Abdominal Operations. 8th ed. 2 vols. Edited by Seymour I. Schwartz, Harold Ellis and Wendy Cowles Husser. Vol. I – 1024 pp. Vol. II – 1265 pp. Illust. Appleton-Century-Crofts, Norwalk, Conn., 1985. Price not stated. ISBN 0-8385-6100-4 (set); ISBN 0-8385-6098-9 (vol. I); ISBN 0-8385-6099-7 (vol. II).

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

Outpatient Urologic Surgery. Keith W. Kaye. 312 pp. Illust. Lea & Febiger, Philadelphia, 1985. $56.50. ISBN 0-8121-0907-4.

continued on page 231

A message from Johnson & Johnson on tapes

Zonas* porous adhesive tape is the highest quality cloth tape available because it was designed for you and your patients.

Zonas* is strong, it lets skin breathe, minimizes skin irritation and leaves minimal adhesive residue.

Pinked edges make it easy-to-tear across and it tears lengthwise without scissors.

And it's cost effective! You won't throw away half-used rolls of Zonas* because it always unwinds to the very

ZONAS* POROUS ADHESIVE TAPE IS MADE IN CANADA

JOHNSON & JOHNSON TAPES

Doing what they do best

*Trademark of JOHNSON & JOHNSON

diachylon poreux
ZONAS*
porous tape

Johnson & Johnson INC

PHILIP H. GORDON, MD, FRCSC, FACS; CAROL-ANN VASILEVSKY, MD

2. Lateral Internal Sphincterotomy: Rationale, Technique and Anesthesia

To determine the role of lateral internal sphincterotomy under local anesthesia in patients with anal fissures, a retrospective review of 133 patients (62 men, 71 women) was conducted. They ranged in age from 19 to 79 years. The open technique described by Sir Alan Parks was adopted, except that the operation was performed under local anesthesia as an outpatient procedure. Associated operations were performed in nine patients (6.5%). Complications, which occurred in seven patients (5.3%), included difficulty controlling flatus, incomplete wound healing and thrombosed external and prolapsing internal hemorrhoids. Relief of pain was prompt. The advantages of this operation are that hospitalization is not necessary, it can be performed under local anesthesia, postoperative discomfort is of short duration and wounds heal quickly. This report supports the use of lateral internal sphincterotomy for patients with a chronic anal fissure.

Une étude rétrospective portant sur 133 malades (62 hommes et 71 femmes) a été menée dans le but de préciser le rôle de la sphinctérotomie latérale interne sous anesthésie locale dans le traitement des fissures anales. Leur âge allait de 19 à 79 ans. On a adopté la technique ouverte décrite par Sir Alan Parks, à ceci près que l'opération a été pratiquée sous anesthésie locale en clinique externe. Des opérations associées ont été faites chez neuf patients (6.5%). Des complications, qui sont survenues chez sept patients (5.3%), ont inclu difficulté à contrôler les gaz intestinaux, cicatrisation incomplète, thrombose des hémorroïdes externes et prolapsus des hémorroïdes internes. Le soulagement de la douleur fut rapide. Les avantages de cette opération résultent du fait que l'hospitalisation n'est pas nécessaire, qu'elle peut être faite sous anesthésie locale, que la gène postopératoire est de courte durée et que la plaie guérit rapidement. Cet article soutient l'utilisation de la sphinctérotomie latérale interne chez les patients souffrant de fissure anale chronique.

From the Department of Surgery, Sir Mortimer B. Davis-Jewish General Hospital, Montreal, PQ

Presented as part of a symposium on outpatient anorectal procedures by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, Calgary, Alta., Sept. 21, 1983

Accepted for publication Nov. 19, 1984

Reprint requests to: Dr. Philip H. Gordon, Sir Mortimer B. Davis-Jewish General Hospital, 3755 Côte Ste-Catherine Rd., Montreal, PQ H3T 1E2

In the development of a fissure in ano, the initiating factor is generally considered to be trauma to the anal canal, in the form of a hard stool.[1] Usually the acute fissure heals, but under certain conditions it persists. One perpetuating factor that is important in the formation of a chronic anal fissure is chronic constipation. This is more likely an associated symptom but may continue to aggravate the anal canal, perpetuating the fissure. Inflammation has also been invoked as a perpetuating factor but this is unlikely because inflammation is no more florid in patients with very long-standing anal fissures than in those with fissures of recent onset. An abnormality of the internal anal sphincter is important. Studies by Nothmann and Shuster[2] demonstrated that, following rectal distension, the normal reflex relaxation of the internal sphincter is followed by an abnormal "overshoot contraction" in patients with anal fissures. This phenomenon may account for the sphincter spasm and explain the pain that occurs during and after defecation. They further demonstrated that following successful treatment of the fissure, the abnormal reflex contraction vanishes. This abnormality should then be considered when trying to arrive at a rationale treatment for the problem.

In 1959, Eisenhammer[3] recommended lateral internal sphincterotomy to treat patients with a chronic fissure in ano, a procedure that was originally described by Brodie[4] in 1835. There are many variations of Brodie's procedure. It may be performed under local or general anesthesia, through a radial or circumferential incision, or using a subcutaneous technique. The muscle may be divided from medial to lateral or vice versa.

Patients

To determine the results obtained with lateral internal sphincterotomy under local anesthesia, we reviewed retrospectively 133 patients with anal fissure. There were 62 men (47%) and 71 women (53%), ranging in age from 19 to 79 years with most being in the third or fourth decades of life.

Technique

We adopted the technique described by Sir Alan Parks.[5] However, we perform this operation under local anesthesia as an outpatient procedure unless there are extenuating circumstances such as an allergy to the local anesthetic.

With the patient in the prone jackknife position, the perianal region is prepared with a disinfectant solution and draped in the usual fashion. With a fine needle, an anesthetic solution of 0.5% xylocaine in 1:200 000 epinephrine or 0.25% bupivacaine in 1:200 000 epinephrine is infiltrated into the left lateral aspect near the anal verge, ensuring that the solution is directed to the level of the dentate line. The area of the fissure is then anesthetized. A Pratt bivalve is inserted into the anal orifice. Should there still be some discomfort, the entire perianal region may be anesthetized. A short incision is made just distal to the intersphincteric groove, which can usually be palpated quite easily. The anoderm is lifted off the underlying internal sphincter to the level of the dentate line and the intersphincteric plane is developed. The full thickness of the internal sphincter is divided from its lower edge to the level of the dentate line using either a pair of Metzenbaum scissors or a scalpel. Hemostasis is obtained with cautery and the wound can be closed with a couple of interrupted sutures of 3-0 chromic catgut.

Results

The symptoms encountered in this series are shown in Table I.

Thirty-one patients had associated problems: hemorrhoids in 24, anal stenosis in 4, Crohn's disease in 2 and syphilis in 1 patient.

Associated operations were performed in nine patients (6.8%). In four, a one- or two-quadrant hemorrhoidectomy was performed and in one of these a hypertrophied anal papilla was excised. In five other patients, associated hypertrophied anal papillae and sentinel piles were excised. Another patient had his condylomata acuminata removed.

Complications occurred in seven patients (5.3%). Three patients had difficulty controlling flatus. In two, the problem was temporary and resolved spontaneously but one patient had uncontrollable flatus for at least 1 year postoperatively; then she was lost to follow-up. There were three patients whose operative site did not heal. One patient was re-examined under general anesthesia and an unusual finding was demonstrated. It was noted during re-exploration that the lowermost portion of the internal sphincter had not been divided at the original sphincterotomy, consequently the wound did not heal (Fig. 1). This problem was easily corrected by completing the incision. Another wound did not heal because the operation was performed on a patient with Crohn's disease. Although the wound did not heal, the patient was asymptomatic. One patient had persistent pain and the fissure did not heal. Consequently, 1 month later a lateral internal sphincterotomy was performed on the opposite side, giving prompt relief of symptoms and complete healing of the fissure. One patient returned the day after the procedure with a complete ring of prolapsed, thrombosed internal hemorrhoids as well as a ring of thrombosed external hemorrhoids. Emergency hemorrhoidectomy was performed and his postoperative course was smooth. Fortunately, no patient suffered postoperatively from hemorrhage, perianal abscesses or fistula in ano. Urinary retention was not encountered.

Table I—Symptoms in 133 Patients With Anal Fissure

Symptom	No. of patients (%)
Pain	133 (100)
Bright red rectal bleeding	74 (55.6)
Straining	22 (16.5)
Pruritus	11 (8.3)
Prolapse	10 (7.5)
Mucus	4 (3.0)

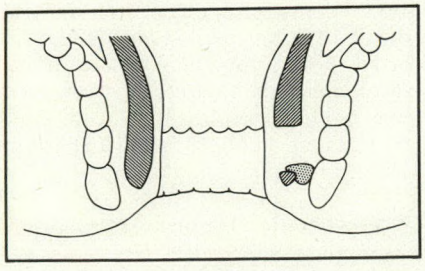


FIG. 1—Incomplete division of lower portion of internal sphincter.

Postoperative Care

Patients were discharged home on a regular diet, advised to take sitz baths and a psyllium seed preparation as a stool softener; a non-constipating oral analgesic was prescribed. Originally, patients were seen 1 week and again 1 month after the procedure, but later in the review it was deemed unnecessary to see them after a week so they were seen only 1 month following the procedure.

Although the exact duration of pain postoperatively was not documented for each patient, most had relief within 48 hours and many within 24 hours.

Table II—Reported Results of Lateral Internal Sphincterotomy

Authors	No.	% impaired control of: Flatus	% impaired control of: Feces	Fecal soiling, %	Unhealed or recurrence, %
Hawley, 1969[6]	24	–	0	0	0
Hoffmann and Goligher, 1970[7]	99	6	1	7	3
Notaras, 1971[8]	82	2	1	6	10
Millar, 1971[9]	99	2	0	1	0
Hunter, 1975[10]	74	27	27	34	12
Rudd, 1975[11]	200	0	0	0	0.5
Oh, 1978[12]	300	1	0.6	2	1.6
Bailey and colleagues, 1978[13]	418	1	1.2	–	1
Marby and colleagues, 1979[14]	78	0	0	0	29
Rosenthal, 1979[15]	125	Few	0	0	0.8
Abcarian, 1980[16]	150	30	0	0	1.3
Vafai and Mann, 1981[17]	272	16	0	12	3
Current series, 1983	133	2.3	0.8	0	1.5

Discussion

In recent years, lateral internal sphincterotomy has increasingly been the treatment of choice for patients with a chronic anal fissure. In a poll of the members of the American Society of Colon and Rectal Surgeons in 1979, most respondants stated that their first or preferred operation of choice for chronic fissure in ano was the lateral internal sphincterotomy. Recently, many authors[6-17] have reported their results with this operation (Table II). With only one exception (Hunter[10]) all reported satisfactory control of flatus and feces. In the series reported by Rosenthal,[15] Abcarian,[16] and Vafai and Mann,[17] all of the problems relating to control of flatus and soiling were only temporary. Fecal soiling was reported in some series but varied in degree of concern in different series. Hoffmann and Goligher[7] studied three procedures — posterior internal sphincterotomy, sphincter stretch and lateral internal sphincterotomy — and, when comparing disturbances of anal continence following these operations, found that lateral internal sphincterotomy fared the best.

In terms of the unhealed fissure or the patient who suffers a recurrence, the results of this operation are quite good. Abcarian[16] compared the results of lateral internal sphincterotomy with fissurectomy and midline sphincterotomy. He found that lateral internal sphincterotomy offered rapid wound healing, a low recurrence rate and no permanent defect in continence, and concluded that it was the treatment of choice. The highest recurrence rates were reported by Marby and associates[14] and Notaras.[8] In both series, the lateral internal sphincterotomies were performed in a blind manner. Oh[12] pointed out that in his series the incidence of recurrence was slightly higher in patients who had sphincterotomy performed in a subcutaneous blind manner than in those who had it performed using an open technique. This may explain the higher recurrence rates in the two cited series. The incidence of recurrence may also be related to the amount of internal sphincter divided.

Conclusions

Our experience, supported by that of others in the literature, strongly suggests that lateral internal sphincterotomy is a good operation for patients with a chronic fissure in ano. It has several definite advantages. There is no need for the patient to be hospitalized. The operation can be performed under local anesthesia. Postoperative discomfort is of short duration and wounds heal quickly. Fecal soiling is not a problem and recurrence following this mode of therapy is uncom-

mon. Thus, less time is lost from work and fewer follow-up visits are required. Because of excellent results, we believe that lateral internal sphincterotomy is the treatment of choice for patients with a chronic anal fissure.

References

1. GOLDBERG SM, GORDON PH, NIVATVONGS S: *Essentials of Anorectal Surgery*, Lippincott, Philadelphia, 1980: 86–99
2. NOTHMANN BJ, SHUSTER MM: Internal anal sphincter derangement with anal fissures. *Gastroenterology* 1974; 67: 216–20
3. EISENHAMMER S: The evaluation of internal anal sphincterotomy operation with special reference to anal fissure. *Surg Gynecol Obstet* 1959; 109: 583–90
4. BRODIE BC: Lectures on diseases of the rectum. III. Preternatural contraction of the sphincter ani. *Lond Med Gaz* 1835; 16: 26–31
5. PARKS AG: The management of fissure-in-ano. *Hosp Med* 1967; 1: 737–8
6. HAWLEY PR: The treatment of chronic fissure-in-ano. A trial of methods. *Br J Surg* 1969; 56: 915–8
7. HOFFMANN DC, GOLIGHER JC: Lateral subcutaneous internal sphincterotomy in treatment of anal fissure. *Br Med J* 1970; 3: 673–5
8. NOTARAS MJ: The treatment of anal fissure by lateral subcutaneous internal sphincterotomy — a technique and results. *Br J Surg* 1971; 58: 96–100
9. MILLAR DM: Subcutaneous lateral internal anal sphincterotomy for anal fissure. Ibid: 737–9
10. HUNTER A: Anorectal problems: lateral subcutaneous anal sphincterotomy. *Dis Colon Rectum* 1975; 18: 665–8
11. RUDD WW: Lateral subcutaneous internal sphincterotomy for chronic anal fissure, an outpatient procedure. Ibid: 319–23
12. OH C: A modified technique for lateral internal sphincterotomy. *Surg Gynecol Obstet* 1978; 146: 623–5
13. BAILEY RV, RUBIN RJ, SALVATI EP: Lateral internal sphincterotomy. *Dis Colon Rectum* 1978; 21: 584–6
14. MARBY M, ALEXANDER-WILLIAMS J, BUCHMANN P, ARABI Y, KAPPAS A, MINERVINI S, GATEHOUSE D, KEIGHLEY MR: A randomized controlled trial to compare anal dilatation with lateral subcutaneous sphincterotomy for anal fissure. *Dis Colon Rectum* 1979; 22: 308–11
15. ROSENTHAL D: Fissure-in-ano management in the military community. *Milit Med* 1979; 144: 505–8
16. ABCARIAN H: Surgical correction of chronic anal fissure: results of lateral internal sphincterotomy vs. fissurectomy — midline sphincterotomy. *Dis Colon Rectum* 1980; 23: 31–6
17. VAFAI M, MANN CV: Closed lateral internal anal sphincterotomy without removal of sentinel pile for fissure-in-ano. *Coloproctology* 1981; 3: 91–3

ZANE COHEN, MD, FRCSC

3. Alternatives to Surgical Hemorrhoidectomy

Hemorrhoids are an extremely common affliction. The prevalence ranges from 1 in 25 to 1 in 30 individuals. There was a 20% decrease in the number of hemorrhoidectomies performed between 1978 and 1982. Alternatives to formal hemorrhoidectomy are injection sclerotherapy and rubber-band ligation. High-fibre diets and bulk laxatives are effective in relieving the symptoms of hemorrhoids, easing defecation and regulating bowel habit and can be used liberally. Bleeding hemorrhoids can be treated by diet alone, or by injection or rubber-band ligation. Prolapsing hemorrhoids are best treated by rubber-band ligation. The relatively few patients in whom these more conservative measures fail can be considered for hemorrhoidectomy.

Les hémorroïdes sont une affection très courante. La prévalence se situe entre 1 sur 25 individus et 1 sur 30. On a constaté une diminution de 20% du nombre des hémorroïdectomies entre 1978 et 1982. La sclérothérapie par injection et la ligature par bande élastique sont des alternatives à l'hémorroïdectomie classique. Les régimes riches en fibres et les laxatifs mucillagineux soulagent efficacement les symptômes des hémorroïdes, facilitent la défécation et régularisent les selles; ils peuvent être largement utilisés. Les saignements hémorroïdaires peuvent être traités par le régime seul, par injection ou par ligature par bande élastique. Le meilleur traitement des hémorroïdes prolabées est la ligature par bande élastique. Les quelques patients pour qui ces mesures conservatrices ne suffisént pas sont candidats à l'hémorroïdectomie.

Hemorrhoidal disease is extremely common in westernized countries. In North America it has been estimated that one out of every two individuals over the age of 40 years has some degree of hemorrhoidal disease. In the third world this prevalence ranges from 1 in 25 to 1 in 30.[1] In the majority of cases the hemorrhoids are asymptomatic. In a study reported by Haas and associates,[2] 198 (82%) of 241 asymptomatic persons were found to have hemorrhoids. For comparison, in the symptomatic group of 594 patients, 522 (88%) had evidence of hemorrhoids.

Asymptomatic hemorrhoids appear with increasing age. The peak ages are from 40 to 80 years. Symptomatic hemorrhoids are similarly distributed although there are a greater number with symptomatic hemorrhoids under the age of 30 years.[3] In Ontario, the prevalence of hemorrhoids is the same as is mentioned above; however, there has been a steady decrease (20%) in the number of hemorrhoidectomies performed from 1978 to 1982.[4] In my own practice over a 6-year period, I have seen 412 patients with hemorrhoidal disease, only 26 of whom required hemorrhoidectomy; 156 underwent rubber-band ligation, 21 injection sclerotherapy and 213 were managed by dietary manipulation alone.

Alternatives to Hemorrhoidectomy

The classifications that I use for hemorrhoids are: first degree — maintained persistently at the proper level in the anal canal; second degree — prolapse with bowel movement but spontaneously reduced when straining ceases; third degree — prolapse out of the anal canal requiring manual reduction; fourth degree — prolapse, often thrombosis, and cannot be reduced manually.

The usual symptoms consist of constipation, bleeding, discomfort, prolapse and occasionally an associated discharge with anal irritation. These symptoms can often be resolved by office treatment of the hemorrhoidal disease using a high-fibre diet, and injection sclerotherapy or rubber-band ligation, or both.

High-Fibre Diet

In 1978, Webster and associates[5] com-

From the Division of General Surgery, Toronto General Hospital, Toronto, Ont.

Presented as part of a symposium on outpatient anorectal procedures by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, Calgary, Alta., Sept. 21, 1983

Accepted for publication Feb. 12, 1985

Reprint requests to: Dr. Zane Cohen, Eaton Building, 9-211, Toronto General Hospital, 101 College St., Toronto, Ont. M5G 1L7

pared the effects of Fybogel and placebo on patients with hemorrhoidal disease. The end points were relief of symptoms, ease of defecation and regular bowel habits. For all of these end points, there was a clear indication that the majority of patients were improved with Fybogel compared to placebo, particularly in those who described greater ease of defecation and better bowel habit. In my own experience, most patients who are compliant and who will agree to be placed on a high-fibre diet supplemented by stool softeners can often minimize their symptoms, particularly if they are complaining of only small amounts of bright red rectal bleeding and anal discomfort on defecation.

Injection Sclerotherapy

The indications for injection sclerotherapy are first-degree hemorrhoids and small second-degree hemorrhoids where the major symptom is that of bleeding. The rationale for injection sclerotherapy is the use of an irritant solution that produces an inflammatory reaction and fibrosis with subsequent devascularization, thus minimizing rectal bleeding.[6] The fibrosis increases the fixation of the hemorrhoid to the underlying muscle thereby also reducing prolapse. Injection sclerotherapy is a simple and safe method for decreasing hemorrhoidal bleeding. The needle should be placed in the submucosal layer well above the dentate margin and 3 to 4 mL of 5% phenol in oil can be used surrounding each of the hemorrhoids. The contraindications are external hemorrhoids, acute attacks of hemorrhoidal disease and repeated injection as well as associated anal lesions. The complications include necrosis and injection ulcers, submucosal abscess and parathenomas.[6] All these complications are rare.

Injection sclerotherapy is more popular in Great Britain than it is in North America. However, in my practice I often inject hemorrhoids when the major symptom is hemorrhoidal bleeding, as I have found that rubber-band ligation can be somewhat inaccurate when the exact site of bleeding is difficult to identify.

Rubber-Band Ligation

Rubber-band ligations can be used for second- and third-degree hemorrhoids, and occasionally following reduction of fourth-degree hemorrhoids. The technique is relatively easy. The discomfort that arises will be minimized if one performs the procedure well above the dentate margin. I prefer to ligate only one or at most two hemorrhoids at each sitting. The ligation of three hemorrhoids will produce substantial pain and discomfort.

Approximately 75% of patients in my practice either have no further symptoms or are greatly improved following one or two rubber-band applications. In a study performed at the Lahey Clinic in 1981 of 266 patients, 113 (43%) had no further symptoms following rubber banding, 69 (26%) were greatly improved, 29 (11%) were mildly improved and 20% were unchanged or worse.[7]

The complications following rubber-band ligation are mainly severe pain in 6% to 10% and hemorrhage in 1% to 2% of patients.[6] Two of my patients returned to hospital with major lower gastrointestinal bleeding from the rubber-band ligation site 10 to 14 days after the procedure. The immediate treatment for this is to place pressure over the area or to insert a Foley catheter, inflate the balloon and pull back to tamponade the bleeding until the bleeding site can be identified and oversewn.

Summary

The treatment of bleeding hemorrhoidal disease is first injection sclerotherapy. The failures are considered for rubber-band ligation. When hemorrhoids are large and protruding, rubber-band ligation is the procedure of choice.

For large prolapsing internal hemorrhoids, an attempt is made to ligate these using rubber bands. If this fails, hemorrhoidectomy is performed.

With conservative measures and the institution of a high-fibre diet and stool softeners, the majority of hemorrhoids can be treated nonsurgically with satisfactory results.

References

1. BURKITT DP: Varicose veins, deep vein thrombosis, and haemorrhoids: epidemiology and suggested aetiology. *Br Med J* 1972; 2: 556–61

2. HAAS PA, HAAS GP, SCHMALTZ S, FOX TA JR: The prevalence of hemorrhoids. *Dis Colon Rectum* 1983; 26: 435–9

3. BURKITT DP: *Haemorrhoids: Epidemiological Features,* Royal Society of Medicine, International Congress and Symposium Series no. 12, Academic Press, London, 1978

4. Data Development and Evaluation Branch, Ontario Ministry of Health, Toronto, Ont., September 1983

5. WEBSTER DJ, GOUGH DC, CRAVEN JL: The use of bulk evacuant in patients with haemorrhoids. *Br J Surg* 1978; 65: 291–2

6. GOLIGHER JC, DUTHIE HL, NIXON HH: *Surgery of the Anus, Rectum and Colon,* 5th ed, Baillière Tindall, London, 1984: 98–149

7. WROBLESKI DE, CORMAN ML, VEIDENHEIMER MC, COLLER JA: Long-term evaluation of rubber ring ligation in hemorrhoidal disease. *Dis Colon Rectum* 1980; 23: 478–82

BOOKS RECEIVED

continued from page 226

Surgical Management. Edited by Selwyn Taylor, Geoffrey D. Chisholm, Niall O'Higgins and Robert Shields. 918 pp. Illust. William Heinemann Medical Books Ltd., London, 1984. $99 (US). ISBN 0-433-32208-X.

Techniques for Surgeons. Edited by J. Patrick O'Leary and Eugene A. Woltering. 442 pp. Illust. John Wiley & Sons, Toronto, 1985. Price not stated. ISBN 0-471-88957-1.

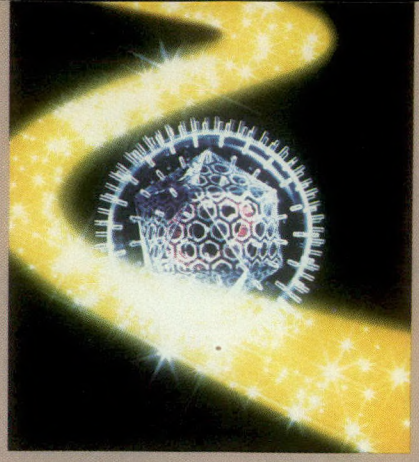
Textbook of Surgery. 5th ed. Edited by David A. Macfarlane and Lewis P. Thomas. 468 pp. Illust. Academic Press Canada, Don Mills, Ont., 1984. $45, paperbound. ISBN 0-443-02768-4.

Ultrasound in Urology. 2nd ed. Martin I. Resnick and Roger C. Sanders. 430 pp. Illust. Williams & Wilkins, Baltimore, 1984. Price not stated. ISBN 0-683-07219-6.

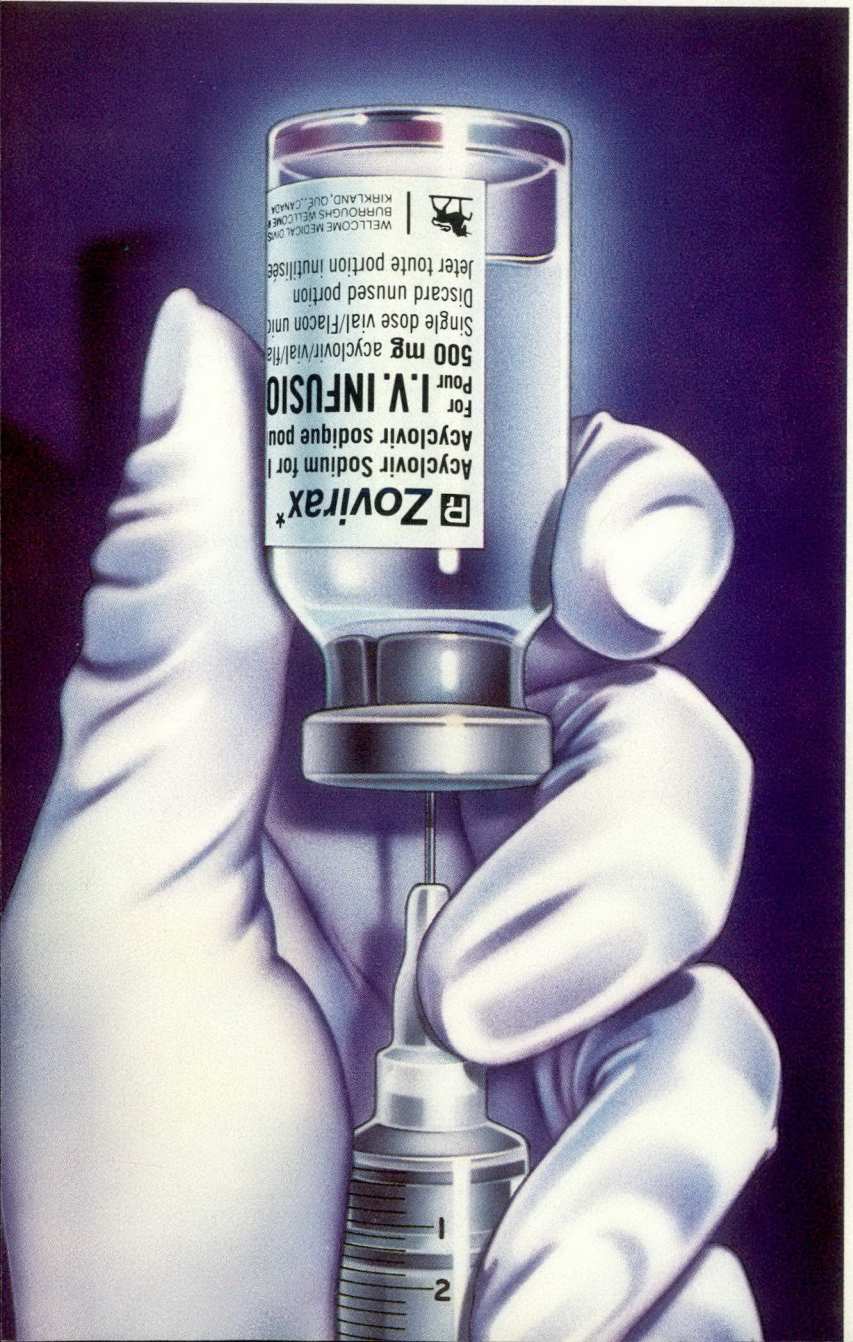
Urinary Stone. Proceedings of the Second International Urinary Stone Conference, Singapore, 1983. Edited by Rosemary L. Ryall, J. Gwynne Brockis, Villis R. Marshall and Birdwell Finlayson. 391 pp. Illust. Churchill Livingstone, Edinburgh; Academic Press Canada, Don Mills, Ont., 1984. $79.50. ISBN 0-443-93014-6.

Vascular and Doppler Ultrasound. Edited by C. Carl Jaffe. 311 pp. Illust. Churchill Livingstone, Edinburgh; Academic Press Canada, Don Mills, Ont., 1984. $40.50. ISBN 0-443-08295-2.

NEW



ZOVIRAX* I.V. INFUSION
(ACYCLOVIR SODIUM)



The first effective anti-herpes therapy is now available in an I.V. infusion for treatment of initial and recurrent mucosal and cutaneous herpes simplex infections in immunocompromised adults and children. It is also indicated for severe initial episodes of herpes simplex infections in immunocompetent patients.

Highly efficacious in controlled clinical studies, ZOVIRAX I.V. selectively blocks the viral replication process and significantly shortens the period of viral shedding.

ZOVIRAX-treated patients become contagion-free faster.

What's more, if therapy is initiated at the earliest possible moment, patients will heal faster and experience significantly less pain.

To date, efficacy has not been complicated or compromised by side effects.

Note: ZOVIRAX I.V. Infusion is for intravenous infusion only.

Therapy is recommended for at least 5 days for immunocompetent patients and for at least 7 days for immunocompromised patients.

Finally . . . ZOVIRAX I.V. INFUSION.

PAAB
CCPP

*Trade Mark
W-2055

WELLCOME MEDICAL DIVISION
BURROUGHS WELLCOME INC.
KIRKLAND, QUÉ.

LEE E. SMITH, MD, FACS

4. Flexible Fiberoptic Sigmoidoscopy: an Office Procedure

Patients who had benign polyps and cancers were studied retrospectively to define whether use of the 60-cm flexible sigmoidoscope would markedly improve the diagnostic yield over the 25-cm rigid sigmoidoscope. Of the polyps found, 48% could have been seen by the rigid sigmoidoscope and 85% by the flexible sigmoidoscope. Cancers were within reach of digital examination in 21%, of the rigid sigmoidoscope in 38% and of the flexible sigmoidoscope in 60%. This verifies the greater diagnostic yield by the flexible sigmoidoscope.

In 211 asymptomatic patients who underwent flexible fiberoptic sigmoidoscopy, the scope reached to 25 cm in all and to 50 cm in 75%. The average time required for the examination was 4.9 minutes. Of these patients, who had also undergone rigid sigmoidoscopy previously, 76% preferred the flexible scope, 18% preferred the rigid scope and 6% could tell no difference. The yield of neoplasms was 4% in the distal 25 cm of the colon and rectum, but an additional 8% were found in the sigmoid colon.

This review supports the need for flexible sigmoidoscopy in the office as a screening tool for detection of polyps and early diagnosis of cancer in the asymptomatic patient over 40 years of age. Technique, costs and complications are discussed.

Afin de vérifier si, par rapport au sigmoïdoscope rigide de 25 cm, un sigmoïdoscope flexible de 60 cm était capable d'améliorer sensiblement l'efficacité diagnostique, l'auteur a étudié en rétrospective une série de patients porteurs de polypes bénins ou de cancers. De tous les polypes découverts, 48% auraient pu être trouvés avec le sigmoïdoscope rigide et 85% avec le sigmoïdoscope flexible. Les cancers étaient à la portée du touché rectal dans 21% des cas, du sigmoïdoscope rigide dans 38% et du sigmoïdoscope flexible dans 60%. Ceci met en évidence la meilleure efficacité diagnostique du sigmoïdoscope flexible.

Parmi 211 patients asymptomatiques soumis à une fibroscopie à l'aide du sigmoïdoscope flexible, l'instrument s'est rendu à 25 cm dans tous les cas et a atteint 50 cm dans 75%. Le temps moyen requis pour l'examen fut de 4.9 minutes. De ceux qui avaient déjà subi un examen au sigmoïdoscope rigide, 76% ont préféré l'instrument flexible, 18% le sigmoïdoscope rigide et 6% n'avaient pas de préférence. Le nombre de néoplasies découvertes dans le 25 cm distal du côlon et du rectum fut de 4% mais un 8% supplémentaire fut découvert dans le sigmoïde.

Cette étude souligne la nécessité d'utiliser le sigmoïdoscope flexible dans le cabinet de consultation comme moyen de dépistage des polypes et pour le diagnostic précoce du cancer chez les patients asymptomatiques de plus de 40 ans. On commente la technique, ses coûts et ses complications.

One in 25 Americans suffers from cancer of the colon at some time. There are approximately 120 000 new cases of colonic and rectal cancer each year, and 60 000 deaths.[1] The number of deaths annually is consistently about half the incidence, reflecting the positive observation that 50% may be cured. However, cure is predicated upon detection of the cancer while it is still localized. Effective screening procedures are necessary to unmask occult cancers.

Is there an effective means of preventing colonic and rectal cancer? Morson[2] demonstrated that there is a sequence of degeneration of the benign, tubular adenoma to cancer. Following this reasoning, the detection and removal of benign tubular or papillary adenomas is the only known means of preventing carcinoma of the colon or rectum. Evidence that this action prevents cancer was provided by Gilbertsen, at the Cancer Detection Clinic of the University of Minnesota.[3] He reported a marked decrease from the predicted number of cancers as a result of detection and removal of all polyps.

If a cancer is detected earlier, is the outcome of the disease influenced? As previously noted, approximately 50% of the patients in whom colonic or rectal cancer is diagnosed can be cured by surgical excision. The cure rates are greatest in those cancers that are small and have not yet metastasized. For example, cases of colonic and rectal cancer recorded at the National Naval Medical Center Tumor Registry in Bethesda, Md., were grouped by the Astler-Coller classification, a modification of Dukes' classification (Table I).[4] The 5-year survival for patients in these groups was as follows: A — 100%, Bl — 77%, B2 — 61%, Cl — 66%, C2 — 30%, D — 1%. Clearly, earlier detection of lesser stages of cancer would positively influence the cure of this disease.

In regard to cancer of the colon, the American Cancer Society has recommended (a) annual digital rectal examination in patients over 40 years of age, (b) annual examination for occult blood in patients over 50 years of age and (c)

Table I—Astler–Coller Classification of Colonic and Rectal Cancer

Class	Description
A	Limited to mucosa.
B1	Extension into but not through muscularis propria, negative nodes.
B2	Extension through muscularis propria, negative nodes.
C1	Extension into but not through muscularis propria, positive nodes.
C2	Extension through muscularis propria, positive nodes.
D	Distant metastases.

From the Department of Surgery, George Washington University, Washington, DC

Presented as part of a symposium on outpatient anorectal procedures by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, Calgary, Alta., Sept. 21, 1983

Accepted for publication Nov. 19, 1984

Reprint requests to: Dr. Lee E. Smith, Associate Professor, Department of Surgery, George Washington University, 2150 Pennsylvania Ave. NW, Washington, DC 20037, USA

← For prescribing information see page 241

sigmoidoscopy every 3 to 5 years in patients over age 50.

The rigid 25-cm sigmoidoscope is the instrument that is referred to in the last recommendation. If rigid sigmoidoscopy offers diagnostic benefit, would more benefit be provided by the flexible sigmoidoscope, which examines up to 60 cm of colon?

This paper addresses the rationale, indication and techniques for using flexible fiberoptic sigmoidoscopy as a primary screening tool in the physician's office.

Method

At the National Naval Medical Center, Bethesda, Md., 499 patients (336 men, 153 women) who had polyps removed through either a rigid sigmoidoscope or colonoscope between 1974 and 1981 had their charts reviewed to determine the site of the lesion. All patients had undergone barium enema examination or colonoscopy as part of the investigation. Lesions up to 25 cm from the anus were designated to be within view of the rigid sigmoidoscope. The remainder were classified as to site by barium enema or colonoscopy. The polypoid lesions were classified as simple tubular, mixed tubular and papillary, papillary, simple tubular with cancer, mixed with cancer, papillary with cancer, or metaplastic. The metaplastic polyps are not believed to have the potential to degenerate into cancer, as opposed to the other polyps.

The charts of 448 patients with cancer from 1970 to 1979 were reviewed to identify the site of the cancer. Cancers within 10 cm were considered reachable by digital examination. Those from 10 to 25 cm were potentially reached by the rigid sigmoidoscope. Those in the sigmoid were potentially within reach of the flexible fiberoptic sigmoidoscope.

In 1979, a subset of 211 asymptomatic patients at the United States Capitol Colon and Rectal Clinic, Washington, DC, were evaluated by flexible fiberoptic sigmoidoscopy. Prospective data regarding level reached in the colon at examination, time required for examination, numbers of lesions identified and patient preference were gathered. Patient preference is meaningful because all patients had previously undergone rigid sigmoidoscopy as part of an annual physical examination. Time was kept by a stop watch; as the scope touched the anus time began, and as the scope was withdrawn from the anus the watch was stopped.

Technique

The procedure is performed during an office visit. Two small enemas are given as preparation. The patient is placed on the power table in the jackknife position but is not tilted into a head-down position. No sedation is necessary. A two-glove technique is used, the outer glove being worn only for digital examination and introduction of the well-lubricated sigmoidoscope. As a matter of personal preference, the scope dial controls were taken out of the locked mode so that the tip would advance freely. The scope is gently pushed blindly up to the 5- to 10-cm level. Under direct vision, the rectum can be traversed to the 15- to 20-cm level easily. The right hand is used to

Table III—Colon and Rectal Cancers in 448 Patients, 1970 to 1979

Level	Potential detection by	No. (%)	Cumulative gain, no. (%)
0–10 cm	Digit	92 (21)	92 (21)
11–25 cm	Rigid scope	78 (17)	170 (38)
Sigmoid	Flexible scope	99 (22)	269 (60)

Table IV—Level of Examination Achieved by Flexible Fiberoptic Sigmoidoscopy in 211 Patients

Level, cm	No. (%)	Cumulative reach, %
10–19	0 (0)	100
20–29	4 (2)	100
30–39	14 (6)	98
40–49	39 (19)	92
50–59	86 (41)	73
⩾ 60	68 (32)	32

Table V—Site of Neoplasms Found by Flexible Fiberoptic Sigmoidoscopy in Asymptomatic Patients

Series	No. of patients	Level, no. (%)		Totals, no. (%)
		< 25 cm	> 25 cm	
Bohlman and associates, 1977[5]	120	8 (6.6)	28 (23.3)	36 (30)
Lipshutz and associates, 1979[6]	200	–	–	– (9.5)
Marks and associates, 1979[7]	203	9 (4.4)	16 (7.8)	25 (12.2)
Meyer and associates, 1979[8]	122	3 (2.4)	13 (10.6)	16 (13)
Wherry, 1981[9]	417	38 (9.1)	35 (8.4)	73 (17.5)
Present study	211	10 (4)	18 (8.0)	14 (12)

Table II—Polyps of the Colon and Rectum in 499 Patients, 1974 to 1981

Site	Polyp type							
	Tubular	Tubular with carcinoma	Mixed	Mixed with carcinoma	Papillary	Papillary with carcinoma	Metaplastic	Totals
Rectum	109	8	32	17	16	5	72	259
Sigmoid	83	6	35	8	3	3	30	168
Descending colon	15	0	2	1	0	0	3	21
Splenic flexure	1	0	0	1	0	1	2	5
Transverse colon	5	0	2	1	1	0	0	9
Hepatic flexure	2	0	2	0	0	2	0	6
Ascending colon	10	0	1	2	3	0	2	18
Cecum	3	0	0	2	5	3	0	13

grasp the sigmoidoscope shaft near the anus, to pull or push and to torque the shaft of the scope. When the tip must be deflected to find the correct direction up the bowel lumen, the right hand is moved to the dials. The left hand supports the scope head, and the fingers are automatically in position to apply suction or insufflation. Often the left thumb, cradling the scope head, is used to rotate a dial, leaving the right hand free to apply torque. Examination is performed as the scope is withdrawn. The examiner leans away from the patient, drawing the scope out slowly. With this extracting action, both hands are free for fine movements of the dials to inspect the bowel wall. Insufflation is important to flatten out folds for more complete examination. Before the scope is removed, all air is suctioned out to decrease distension and the feeling of bloating that the patient experiences.

Results

Of the 499 patients who had polyps removed at the National Naval Medical Center between 1974 and 1981, 390 had epithelial neoplasms (tubular, mixed or papillary) and 109 had metaplastic polyps (Table II). Because metaplastic polyps do not degenerate into cancers, our attention focused on the tubular and papillary polyps. Of these neoplasms, 187 (48%) were in the rectum and presumably could be seen by the rigid sigmoidoscope. There were 138 (35%) in the sigmoid, which could have been reached by the flexible fiberoptic sigmoidoscope.

The retrospective review of the charts of 448 patients with colonic and rectal cancer seen between 1970 and 1979 revealed that 92 (21%) of the tumours were within reach of digital examination, 170 (38%) within reach of the rigid sigmoidoscope and 269 (60%) within reach of the flexible sigmoidoscope (Table III).

Of the 211 asymptomatic patients at the United States Capitol Colon and Rectal Clinic who underwent flexible sigmoidoscopy, all were examined up to the 25-cm level, which could be examined by the rigid sigmoidoscope (Table IV). Seventy-seven percent were examined to the 50-cm level and higher.

The average time required to complete flexible fiberoptic sigmoidoscopy was 4.9 minutes (range from 3 to 10 minutes). The patient preference for rigid sigmoidoscopy was 38 (18%) and for flexible sigmoidoscopy 160 (76%); 13 (6%) had no preference. Twenty-eight of the asymptomatic patients had neoplasms. Only 10 of these were below the 25-cm level, within reach of the rigid sigmoidoscope (Table V[5-9]).

Table VI—Level Reached by Flexible Fiberoptic Sigmoidoscopy

Series	No. of patients	Level, %	
		< 25 cm	> 45 cm
Bohlman and associates, 1977[5]	139	–	50
Manier, 1978[12]	140	100	67
Crespi and associates, 1978[13]	468	–	63
Lambert and associates, 1978[14]	300	95	50
Marks and associates, 1979[7]	1012	99	66
Winawer and associates, 1979[15]	108	94	46
Winnan and associates, 1980[16]	342	99	52
Present study	211	98	73

Table VII—Mean Level Reached by Rigid Sigmoidoscopy

Series	No. of patients	Mean level, cm
Bohlman and associates, 1977[5]	139	20.4
Marks and associates, 1979[7]	1012	20.0
Winnan and associates, 1980[16]	243	20.0
Nivatvongs and Fryd, 1980[17]	500 men	> 20
	500 women	18

Table VIII—Degree of Discomfort Caused by Flexible Fiberoptic Sigmoidoscopy

Series	No. of patients	Pain, %		
		None	Minimal to moderate	Severe
Lambert and associates, 1978[14]	300	–	–	3.6
Marks and associates, 1979[7]	1012	–	–	10.8
Winnan and associates, 1980[16]	342	–	80.0	20.0
Traul and associates, 1983[18]	5000	31	68.4	0.6

Table IX—Time Required for Flexible Fiberoptic Sigmoidoscopy

Series	No. of patients	Mean time, min
Bohlman and associates, 1977[5]	139	9.4
Crespi and associates, 1978[13]	468	6
Lambert and associates, 1978[14]	300	5.15
Lipshutz and associates, 1979[6]	200	7.5
Marks and associates, 1979[7]	1012	5
Present study	211	4.9

Discussion

A longer sigmoidoscope for screening has become necessary, because the location of cancers has gradually shifted to sites higher in the colon.[10,11] Formerly, it was believed that the rigid sigmoidoscope would detect over half of the cancers, whereas today, that number is only one third. The sigmoid colon now accounts for 30% of colonic and rectal cancers, a rate that previously was only 13%. A review of the literature reveals that the distal 25 cm of the rectum and colon are examined with the flexible sigmoidoscope in over 94% of cases (Table VI[5,7,12-16]). The 45- to 50-cm level is achieved in 46% to 79% of patients in the same series; that doubles or triples the length of bowel examined by the rigid sigmoidoscope.

The rigid sigmoidoscope has gained a reputation as a torture instrument. Seldom is the full 25 cm of the rigid sigmoidoscope inserted, because patient tolerance is poor. The mean level reached has been reported by several authors to be approximately 20 cm (Table VII[5,7,16,17]). However, Nivatvongs and Fryd[17] stated that the 20-cm level applies to men, the mean level reached in females being only 18 cm. A less painful procedure will allow a better examination.

Several authors have described severe patient discomfort, requiring examination with the flexible fiberoptic sigmoidoscope to be stopped. Severely painful examinations range from 0.6% to 20% (Table VIII[7,14,16,18]). This wide range reflects the

difficulty in evaluating such a subjective complaint as pain. A review of the literature shows that the yield of neoplasms when screening asymptomatic patients with the longer, less-painful flexible sigmoidoscope is about 12% (Table V). Many of the benign neoplasms are potential cancers that have been prevented by early detection and excision.

What is the cost in terms of time and money? As experience is gained, the endoscopist will be able to perform the procedure quicker. For inexperienced endoscopists, double the appointment time must be allotted so that eye–hand coordination can be practised and the frustration of racing the clock can be avoided. The literature suggests that when the endoscopist is familiar with the procedure, the time required will average 5 to 6 minutes (Table IX[5-7,13,14]).

The initial cost of equipment is over $2500 for a complete system, and if repair is required, costs are high. However, the flexible fiberoptic sigmoidoscopes have proved to be quite durable. Over 600 uses can be expected, and often up to 1000 examinations can be performed before the equipment fails.

An additional cost is the need for an assistant to set up the scope, to help steady the scope during insertion and to clean it.

The fee for flexible fiberoptic sigmoidoscopy, as for other procedures, varies around the United States. It is usually two to three times the cost of sigmoidoscopy with a rigid scope. Double the cost of sigmoidoscopy is reasonable, because twice as much bowel is examined, twice as many lesions are found, twice as much time is required and perhaps twice the risk is incurred.

Complications have been rare. Hemorrhage and perforation are the major possible complications. Hemorrhage occurs more easily in the presence of existing disease with friable mucosa. Stretching a loop of sigmoid can result in splitting the bowel wall, causing hemorrhage or perforation. This is prevented by avoiding force on the scope. The culprit is often the slide-by technique, which everyone uses to some degree. This technique results in entrapment of the tip against the bowel wall, which is recognized as a "red out" by the endoscopist. Continued pushing may cause a perforation. Such conditions as acute inflammatory bowel disease and radiated or ischemic bowel cause an abnormally weak colonic wall, and very gentle handling of the scope is necessary. Fixed points in the sigmoid, such as adhesions from previous pelvic surgery, may tear easily.

The flexible sigmoidoscope is a diagnostic instrument. Polypectomy should not be attempted without complete bowel preparation, as for colonoscopy, because explosive gases such as methane and hydrogen may be present and may explode if a spark is generated.

The flexible fiberoptic sigmoidoscope is not a substitute for the barium enema or colonoscope. When a patient has symptoms referable to the colon or is in a high-risk group of persons, such as those with polyposis syndromes or chronic ulcerative colitis or having a family history of cancer, complete examination of the colon is indicated.

The ideal candidate for flexible fiberoptic sigmoidoscopy as an office screening procedure is the asymptomatic person over 40 years of age who is not expected to need colonoscopy.

I thank Lisa D. Miller, my research technician, for compiling the data on cancers and polyps.

References

1. SILVERBERG E: Cancer statistics, 1982. *CA* 1982; 32: 15-31
2. MORSON B: President's address. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 1974; 67: 451-7
3. GILBERTSEN VA: Proctosigmoidoscopy and polypectomy in reducing the incidence of rectal cancer. *Cancer* 1974; 34(suppl): 936-9
4. ASTLER VB, COLLER FA: Prognostic significance of direct extension of carcinoma of colon and rectum. *Ann Surg* 1954; 139: 846-52
5. BOHLMAN TW, KATON RM, LIPSHUTZ GR, MCCOOL MF, SMITH FW, MELNYK CS: Fiberoptic pansigmoidoscopy. An evaluation and comparison with rigid sigmoidoscopy. *Gastroenterology* 1977; 72(4 pt 1): 644-9
6. LIPSHUTZ GR, KATON RM, MCCOOL MF, MAYER B, SMITH FW, DUFFY T, MELNYK CS: Flexible sigmoidoscopy as a screening procedure for neoplasia of the colon. *Surg Gynecol Obstet* 1979; 148. 19-22
7. MARKS G, BOGGS HW, CASTRO AF, GATHRIGHT JB, RAY JE, SALVATI E: Sigmoidoscopic examinations with rigid and flexible fiberoptic sigmoidoscopes in the surgeon's office: a comparative prospective study of effectiveness in 1,012 cases. *Dis Colon Rectum* 1979; 22: 162-8
8. MEYER CT, MCBRIDE WJ, GOLDBLATT RS, BORAK J, MARIGNANI P, CONTINO C, MCCALLUM RW: Flexible sigmoidoscopy in asymptomatic patients (abstr). *Gastrointest Endosc* 1979; 25: 43
9. WHERRY DC: Screening for colorectal neoplasia in asymptomatic patients using flexible fiberoptic sigmoidoscopy. *Dis Colon Rectum* 1981; 24: 521-2
10. ROSATO FE, MARKS G: Changing site distribution patterns of colorectal cancer at Thomas Jefferson University Hospital. *Dis Colon Rectum* 1981; 24: 93-5
11. SNYDER DN, HESTON JF, MEIGS JW, FLANNERY JT: Changes in site distribution of colorectal carcinoma in Connecticut, 1940-1973. *Am J Dig Dis* 1977; 22: 791-7
12. MANIER JW: Fiberoptic pansigmoidoscopy: an evaluation of its use in an office practice. *Gastrointest Endosc* 1978; 24: 119-20
13. CRESPI M, CASALE V, GRASSI A: Flexible sigmoidoscopy: a potential advance in cancer control. Ibid: 291-2
14. LAMBERT R, OLIVE C, MELANGE M, CHABANON R: Flexible rectosigmoidoscopy in the detection of tumoral colonic lesions. *Endoscopy* 1978; 10: 284-8
15. WINAWER SJ, LEIDNER SD, BOYLE C, KURTZ RC: Comparison of flexible sigmoidoscopy with other diagnostic techniques in the diagnosis of rectocolon neoplasia. *Dig Dis Sci* 1979; 24: 277-81
16. WINNAN G, BERCI G, PANISH J, TALBOT TM, OVERHOLT BF, MCCALLUM RW: Superiority of the flexible to the rigid sigmoidoscope in routine proctosigmoidoscopy. *N Engl J Med* 1980; 302: 1011-2
17. NIVATVONGS S, FRYD DS: How far does the proctosigmoidoscope reach? *N Engl J Med* 1980; 303: 380-2
18. TRAUL DG, DAVIS CB, POLLOCK JC, SCUDAMORE HH: Flexible fiberoptic sigmoidoscopy — the Monroe Clinic experience. A prospective study of 5000 examinations. *Dis Colon Rectum* 1983; 26: 161-6

Chairman: P. BELLIVEAU, MD, FRCSC*
Panelists: Z. COHEN, P.H. GORDON, E.P. SALVATI, L.E. SMITH

5. Panel Discussion

Dr. Belliveau: I would like to thank the speakers for their excellent presentations and would welcome questions from the audience. While we are waiting, I would ask Dr. Cohen, who spoke on alternatives to hemorrhoidectomy, to tell us if he would consider banding in cases of acute, thrombosed, internal hemorrhoids.

Dr. Cohen: In such a case, I would be conservative and would not use rubber banding on the patient.

Question: When performing left internal sphincterotomy, do you do anything about the sentinel tag and the hypertrophied papilla that we see in chronic fissure in ano?

Dr. Gordon: For the most part I don't. I don't believe that it is necessary for healing of the fissure to excise the hypertrophied anal papilla or the sentinel pile. Occasionally if a patient has a very large pile and complains that it is pushing out and is very bothersome, I may excise it, but in terms of the procedure being necessary to heal a fissure, no. I don't remember the exact number, but I don't think that in my 133 cases, I performed more than six such excisions.

Question: Dr. Salvati, first, what do you do with the chronically unhealed pilonidal wound, especially one that is deep in the interanal cleft near the anal verge? Then a question for Dr. Cohen: I noticed on your slides that you band the hemorrhoid directly and I wonder how many of the members of the panel actually band the hemorrhoid or include the prolapsing tissue and the mucosa above the hemorrhoid.

Dr. Salvati: I think we all have problems with unhealed wounds, particularly if they have been operated on a couple of times. Most of these wounds will heal if you are persistent and see that, first, you make the wound flat, second, that you have the patient use a Water Pik to keep the wound really clean and third, that you see them every week to shave the hair back. If you pay close attention to these points, you can eventually get the sinus healed. The technique described by Rosenberg of reverse strapping helps occasionally. To reverse strap the buttocks is to open the buttocks up. This will sometimes help in difficult cases.

Dr. Cohen: To answer your question, yes, I agree with you. I usually would try to get the upper portion of the hemorrhoid and the prolapsing tissue above it.

Question: May I ask the panel if anyone uses a topical agent, such as Preparation H, on the symptomatic hemorrhoid?

Dr. Salvati: No, if you are talking about symptomatic hemorrhoids. Most of the symptomatic hemorrhoids that we see are thrombosed externally. For every patient with bleeding and protrusion there are many more with thrombosed external hemorrhoids. We ought to point out that the classification Dr. Cohen gave us is for internal hemorrhoids, which don't cause pain unless they are irreducibly prolapsed. They give rise to bleeding and protrusion; pain from hemorrhoidal disease comes from thrombosed external hemorrhoids and they must be excised.

Question: I sometimes have difficulty with patient compliance when I advise a high-fibre diet and I would like to poll the panel and ask them (a) what do they tell their patients and advise them to eat and (b) how do they maintain them?

Dr. Cohen: First, I think it is important to have some kind of dietary regimen to give the patient and instructions about various foods. If the patient has any problem understanding what we are trying to say, we send them to our dietician who works quite closely with us. She will follow them up usually by seeing them every week for the first few weeks to ensure that they have adhered to their diet. I see them within 3 or 4 weeks to assess their progress, and I think by frequent follow-up you can maintain that person not only on high-fibre diet but on stool softeners if indicated.

Dr. Salvati: If you wish to give the patient a high-fibre diet for hemorrhoids and after 6 months or a year those hemorrhoids are still bleeding, they will continue to bleed. You can only keep them asymptomatic just so long; then they will give trouble and you will have to either ligate or inject them. If you prescribe a high-fibre diet for constipation, you can motivate the patient just a little bit better. Searle puts out a booklet of high-fibre items that the patient should eat and you can generally motivate them properly, but it's not easy.

Dr. Gordon: I had a dietician list a whole series of foods and explain how much fibre there was in each food in the categories of various cereals (bran being the best), fruits and vegetables, so that the patients, by the end of the day, would have an idea of how much fibre they were consuming, depending upon what they had eaten from each category. This didn't confine the patients to any one food or any one category of foods but it gave them an idea of which foods were highest in fibre and I think that this has been quite helpful.

Dr. Smith: In general, I tell the patient to go to a health-food store and buy raw unmilled bran. It costs about a dollar a pound. It's about the cheapest thing you can buy. It isn't really tasty, but they must try to disguise it — add it to soups, to salads, to yoghurt, add milk and sugar, fruit, be innovative. They should use a third of a cup a day, measure it out in the morning and by the end of the day it should be finished.

Dr. Belliveau: Dr. Gordon, if you do a lateral sphincterotomy in the office, first of all, I suppose, you don't put any packing in?

Dr. Gordon: None at all.

Dr. Belliveau: And what do you tell your patients to do in the first 2 days if they have pain?

Dr. Gordon: I suggest they take sitz baths. Warm baths are helpful. I prescribe a nonconstipating agent, that is to say one that doesn't have codeine in it. Most of the pain is on the first day; after that, there really is not a lot of dis-

---

Presented as part of a symposium on outpatient anorectal procedures by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, Calgary, Alta., Sept. 21, 1983

Accepted for publication Mar. 1, 1985

**Assistant Professor, Department of Surgery, McGill University, Royal Victoria Hospital, Montreal, PQ*

Reprint requests to: Editorial Office, Canadian Journal of Surgery, *PO Box 8650, Ottawa, Ont. K1G 0G8*

comfort. In fact, some patients who have had a lot of problems with the fissure will say that even their first bowel movement after the operation hurt them less than having the fissure itself.

Dr. Belliveau: Panelists, what do you do if you have a patient who has a fissure associated with hemorrhoids? Do you still do your sphincterotomy in the office or would you suggest something else?

Dr. Smith: Well, everyone has hemorrhoids, it's just a question of whether they are symptomatic or not. I don't do anything if they aren't symptomatic. Depending on the degree of prolapse of the internal hemorrhoids, I will band some subsequently or, if they are what I call third degree hemorrhoids that require manual reduction, I will do a hemorrhoidectomy at the same time.

Dr. Salvati: I believe that if you have a third degree hemorrhoid and a fissure, then you should operate on that particular patient because of what Dr. Gordon has pointed out. After all, if a patient comes to you in pain and you do a lateral sphincterotomy and all the hemorrhoids prolapse, you are going to end up operating anyhow, so you are far better off doing the hemorrhoidectomy for the third and fourth degree hemorrhoids and the lateral sphincterotomy at the same time.

Dr. Cohen: I agree with that, if you have an active fissure and third or fourth degree hemorrhoidal disease.

Question: Dr. Salvati, is there any place left for primary excision of pilonidal disease? And, secondly, when do you operate on a mass as was shown with the acutely prolapsed, thrombosed hemorrhoid?

Dr. Salvati: I really don't see any indication for primary excision and closure. That requires generally a week of hospitalization. It's just too costly and the recurrence rate is high. As far as treating the acute hemorrhoidal prolapse, we described a method a number of years ago in which, if you add 1 mL of hyaluronidase to 10 mL of marcaine or lidocaine, and inject it directly into the edematous mass, you can reduce the internal hemorrhoids within 30 or 40 seconds; then you must excise any external components that are thrombosed. Then you can do multiple internal hemorrhoidal ligations, two, three or four at the same sitting, so you can very easily treat acute hemorrhoidal disease (i.e., prolapsed, thrombosed, gangrenous hemorrhoids) as an office procedure. We do it all the time.

Dr. Belliveau: I would like to summarize briefly what was said this morning. It seems that pilonidal disease can be treated in the office by a simple laying-open procedure under local anesthesia. Lateral internal sphincterotomy should replace anal dilatation for the treatment of anal fissure and that also can be done in the office. As alternatives to hemorrhoidectomy, rubber-band ligation seems to be faring the best and may be followed by injection sclerotherapy. Finally, flexible sigmoidoscopy seems to be something to be explored. I don't think it's the recommendation of Dr. Smith that we should all run out and buy one; the rigid scope still has a role to play, but if you are screening asymptomatic patients, you should consider adding this to your armamentarium. I would like to thank the panel and the audience for their participation.

In the Next Issue

The July 1985 issue of the Journal will contain a number of papers presented at the 1984 annual meeting of the Canadian Cardiovascular Society and at the 1984 annual meeting of the Canadian Association of General Surgeons. Also included will be two papers (one on the management of pancreatic trauma and the other a report from a community hospital on fatal sepsis after splenectomy) originating from the 1984 annual meeting of the Trauma Association of Canada.

NEW ZOVIRAX* (ACYCLOVIR SODIUM) I.V. INFUSION

Now, the first effective anti-herpes therapy is available in an I.V. infusion form: Indicated for immunocompromised adults and children with initial or recurrent mucosal or cutaneous herpes simplex infections ...and for normal patients with severe initial episodes of herpes simplex infections.

ZOVIRAX
(ACYCLOVIR SODIUM)
I.V. INFUSION

ACTIONS

ZOVIRAX (acyclovir), an acyclic nucleoside analog, is a substrate specific for herpesvirus-specified thymidine kinase. It inhibits replication of these viruses. Normal cellular thymidine kinase does not effectively utilize acyclovir as a substrate. Herpesvirus-specified thymidine kinase transforms acyclovir to its monophosphate which is then transformed by cellular enzymes to acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate is both an inhibitor of, and a substrate for, herpesvirus-specified DNA polymerase. Although the cellular α-DNA polymerase in infected cells may also be inhibited by acyclovir triphosphate, this occurs only at concentrations of acyclovir triphosphate which are higher than those which inhibit the herpesvirus-specified DNA polymerase. Acyclovir is preferentially taken up and selectively converted to its active form by herpesvirus-infected cells. Thus, acyclovir has a very much lower toxic potential for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase has a lower affinity for the active form of the drug.

INDICATIONS AND CLINICAL USE

ZOVIRAX Sterile Powder is indicated for treatment of initial and recurrent mucosal and cutaneous herpes simplex infections in immunocompromised adults and children. It is also indicated for severe initial episodes of herpes simplex infections in patients who may not be immunocompromised. It is not recommended for use in herpes encephalitis or other herpes group infections all of which are still the subject of ongoing investigations.

The indications are based on the results of a number of double-blind, placebo-controlled studies which examined changes in virus excretion, total healing of lesions, and relief of pain. Because of the wide biological variations inherent in herpes simplex infections, the following summary is presented merely to illustrate the spectrum of responses observed to date. As in the treatment of any infectious disease, the best response may be expected when the therapy is begun at the earliest possible moment.

In patients experiencing initial episodes of herpes genitalis, virus excretion had ceased in 100% of initial lesions within 3 days after the start of a 5-day course of intravenous ZOVIRAX therapy. Only 20% of placebo recipients were virus-free at this time, as well as when therapy was discontinued. ZOVIRAX therapy arrested virus excretion in over 90% of immunocompromised patients with mucocutaneous disease at the end of 7 days of therapy, while only 26% of placebo-treated patients were virus negative at the same time.

Because complete re-epithelialization of herpes-disrupted integument necessitates recruitment of several complex repair mechanisms, the physician should be aware that the disappearance of visible lesions is somewhat variable and will occur later than the cessation of virus excretion. In spite of these limitations, 100% of ZOVIRAX-treated patients with initial episodes of herpes genitalis healed within 15 days after initiation of treatment. Only 50% of placebo recipients were healed at this same interval. The lesions of 61% of immunocompromised patients who received ZOVIRAX were healed within 15 days after the initiation of a 7-day course of therapy; only 38% of placebo patients had healed their lesions at that point.

Pain associated with herpes infections is highly variable in frequency and intensity. These clinical studies, however, demonstrated that ZOVIRAX therapy plays a significant role in reduction of pain in cutaneous herpes infections in immunocompromised patients. For example, 61% of ZOVIRAX-treated immunocompromised patients were pain-free by day 10, whereas 44% of placebo-treated patients were pain-free in the same period of time.

Whereas cutaneous lesions associated with herpes simplex infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis.

CONTRAINDICATIONS

ZOVIRAX Sterile Powder is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS

ZOVIRAX Sterile Powder should not be administered by any route [i.e. topically (skin or eye), intramuscularly, orally or subcutaneously] other than by intravenous infusion.

PRECAUTIONS

Precipitation of ZOVIRAX crystals in renal tubules can occur if maximum solubility (1.3 mg/mL in water) is exceeded. This phenomenon is reflected by a rise in serum creatinine and blood urea nitrogen and a decrease in creatinine clearance. With sufficient renal tubular compromise, urine output decreases.

Acute increases in serum creatinine and decreased creatinine clearance have been observed in humans receiving ZOVIRAX and: (1) who were poorly hydrated; (2) who were receiving concomitant nephrotoxic drugs (e.g., amphotericin B, and aminoglycoside antibiotics); (3) who had pre-existing renal compromise or damage; and (4) in whom the dose was administered by rapid intravenous injection (less than 10 minutes). Observed alterations in renal function have been transient, in some instances resolving spontaneously without change in ZOVIRAX dosing regimen. In other instances, renal function improved following increased hydration, dosage adjustment, or discontinuation of ZOVIRAX therapy.

When dosage adjustments are required they should be based on estimated creatinine clearance (See DOSAGE AND ADMINISTRATION).

It is not known whether acyclovir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOVIRAX is administered to a nursing mother.

All animal studies carried out to date on reproduction and teratology have been negative. However, since animal reproduction studies are not always predictive of human response, ZOVIRAX should be used during pregnancy only if the physician feels the benefit will outweigh the possible harm to the fetus.

There exists no data, at this time, which demonstrates that the use of ZOVIRAX will prevent transmission of herpes simplex infection to other persons.

Consideration should be given to an alternative treatment regimen if after 5 days of treatment there is no expected clinical improvement in the signs and symptoms of the infection.

Strains of herpes simplex virus which are less susceptible to ZOVIRAX have been isolated from herpes lesions and have also emerged during intravenous treatment with ZOVIRAX.

ADVERSE REACTIONS

The most frequent adverse reactions reported during controlled clinical trials of acyclovir were inflammation or phlebitis (14%) at the injection site following infiltration of the I.V. fluid, and rash or hives (4.7%). Of the patients receiving placebo, 4.8% experienced the same reactions (inflammation/phlebitis, rash or itching).

Less frequent adverse reactions were diaphoresis, hematuria, hypotension, headache and nausea, each of which occurred in 1.6% of the patients. Hematuria and nausea were experienced by placebo recipients at the same frequency. These reactions were observed in severely immunocompromised patients who often have multisystem diseases unrelated to herpes infections and, therefore, it is difficult to state conclusively that these reactions were caused by ZOVIRAX therapy.

Additional adverse reactions were reported in uncontrolled trials. The most frequent adverse reaction was elevated serum creatinine. This occurred in 9.8% of patients, usually but not always following rapid (less than 10 minutes) intravenous infusion. It is not known whether this phenomenon is drug related but in view of the fact that the drug is known to crystallize in urine there exists a possibility that this occurred due to inadequate hydration of the patients. Less frequent adverse experiences were thrombocytosis (0.4%) and jitters (0.4%).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No acute massive overdosage of the intravenous form has been reported.

Doses administered to humans have been as high as 1200 mg/m^2 (28 mg/kg) three times daily for up to two weeks. Peak plasma concentrations have reached 80 μg/mL. Possible evidence of central nervous system (CNS) toxicity (coarse tremors, confusion and agitation) and/or bone marrow toxicity were seen in four patients at 2100 and 2700 mg/m^2/day. The CNS side effects resolved upon lowering the dosage or discontinuing ZOVIRAX therapy. Precipitation of acyclovir in renal tubules may occur when the solubility (1.3 mg/mL) in the intratubular fluid is exceeded. Precipitation may be avoided or overcome by adequate hydration of the patient. Acyclovir is dialyzable. In the event of acute renal failure and anuria, hemodialysis should be initiated until renal function is restored.

DOSAGE AND ADMINISTRATION

CAUTION – RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION ARE TO BE AVOIDED.

Therapy is recommended for at least 5 days for immunocompetent patients and for at least 7 days for immunocompromised patients.

Adults: 5 mg/kg infused at a constant rate over a 1-hour period, every 8 hours (15 mg/kg/day) in patients with normal renal function.

Children Under 12 Years: In children under 12 years of age, more accurate dosing can be attained by administering 250 mg/m^2 infused at a constant rate over a 1-hour period, every 8 hours (750 mg/m^2/day).

Patients with Acute or Chronic Renal Impairment: Use the recommended doses and methods of administration; and adjust the dosing interval as indicated in the following table.

Creatinine Clearance (mL/min/1.73m^2)	Dose (mg/kg)	Dosing Interval (hours)
>50	5	8
25-50	5	12
10-25†	5	24
0-10†	2.5	24-48

†**Hemodialysis:** For patients who require hemodialysis, the mean plasma half-life of acyclovir during dialysis is approximately 5 hours, which results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Recommended doses should be administered every 24-48 hours, and after hemodialysis.

PHARMACEUTICAL INFORMATION

Reconstitution

Reconstitute as follows:

Solutions for Reconstitution

Sterile Water for Injection

Reconstitution Table

Vial Size	Volume to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
500 mg	10 mL	10 mL	50 mg/mL

SHAKE WELL UNTIL DISSOLVED. ASSURE COMPLETE DISSOLUTION BEFORE MEASURING AND TRANSFERRING EACH INDIVIDUAL DOSE.

Intravenous Infusion: The calculated dose of the reconstituted solution should be removed and added to an appropriate intravenous solution listed below at a volume selected for administration during each 1-hour infusion. Infusion concentrations exceeding 10 mg/mL are not recommended. Since the vials do not contain any preservatives any unused portion of the reconstituted solution should be discarded.

Solutions for I.V. Infusion

5% Dextrose Injection
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose and 0.2% Sodium Chloride Injection
Ringer's Injection
Normal Saline Injection
Lactated Ringer's Injection

Stability of Solution

Storage: Reconstituted solutions at a concentration of 50 mg/mL should be used within 12 hours if kept at room temperature. Refrigeration may result in the formation of a precipitate which will redissolve at room temperature.

Once diluted, the admixtures are to be administered within 24 hours of the preparation. The admixtures are not to be refrigerated.

Incompatibility: ZOVIRAX should not be added to biologic or colloidal fluids (e.g. blood products, protein hydrolysates or amino acids, fat emulsions, etc.).

DOSAGE FORMS

Availability: ZOVIRAX is available as sterile powder in 10 mL vials, each containing acyclovir sodium equivalent to 500 mg of acyclovir.

Storage: ZOVIRAX should be stored at 15°-30°C.

Product Monograph available on request.

PAAB CCPP

*Trade Mark

W-2055

WELLCOME MEDICAL DIVISION
BURROUGHS WELLCOME INC.
KIRKLAND, QUÉ.

Symposium: Breast Cancer 1984, Precancerous and High-Risk Lesions

Introduction

Every surgeon has, at some time, encountered the clinical problem of a small focus of abnormal, possibly precancerous tissue in a breast biopsy specimen that contains mainly benign fibrocystic disease. These foci may be atypical hyperplasia, lobular carcinoma in situ or intraductal carcinoma. Traditionally, these diagnoses are considered together and, until recently, were treated quite aggressively by surgical management.

The proper management of these lesions is now questioned, especially because of the evolving pattern of surgical treatment for frank, invasive carcinoma. There has been a trend, based on ongoing scientific evaluation, to abandon the more radical operations and move through a series of steps from radical mastectomy to modified radical mastectomy to partial mastectomy for local control of the breast tumour.

If, as may appear, partial mastectomy is equivalent to total mastectomy for a carcinoma, is it appropriate to consider total mastectomy for precancerous lesions?

In the symposium that follows, input has been sought from epidemiology, pathology and surgery. While there may be some overlap in the statistics cited, the differences in interpretation and in recommendations will be largely because our data base is not sufficiently complete for us to draw definitive conclusions. Therefore, the material presented here is offered not as guidelines for clinical management but as thoughtful and logical appraisals of the available knowledge, to help clinicians work towards better patient management.

RICHARD G. MARGOLESE, MD, FRCSC

Symposium chairman

Department of Surgery,
Sir Mortimer B. Davis-
Jewish General Hospital,
Montreal, PQ
H3T 1E2

MARTIN T. SCHECHTER, MD, M SC, PH D

1. Breast Cancer Risk Factors: Can We Select Women for Prophylactic Mastectomy?

Prophylactic procedures to prevent disease in women at high risk for breast cancer should be considered only when the benefits of prophylaxis outweigh its costs. The rational prophylactic use of mastectomy in these circumstances must await answers to several questions. First, accurate estimates of the true risk associated with these lesions must be obtained, as current estimates are imprecise and potentially biased. Second, large ongoing trials of breast cancer screening and treatment may provide effective methods of distinguishing those women at exceptionally high risk in whom such procedures may be warranted. Finally, the question of conservative surgery as an acceptable treatment for breast cancer must be settled; otherwise, the prophylactic procedure may be more invasive and disfiguring than the treatment of the disease it seeks to prevent.

Les interventions prophylactiques destinées à prévenir le cancer du sein chez les femmes à haut risque ne devrait être envisagées que quand les bénéfices escomptés l'emportent sur les coûts. L'utilisation raisonnable de la mastectomie prophylactique dans ces circonstances doit attendre les réponses à plusieurs questions. Tout d'abord, il faudra établir une évaluation précise des risques réels rattachés à ces lésions puisque les estimations actuelles sont imprécises et possiblement partiales. En second lieu, les importants essais cliniques sur le dépistage et le traitement du cancer du sein feront peut-être ressortir des méthodes efficaces permettant d'identifier les femmes à risque exceptionnellement élevé chez qui de telles interventions pourraient être justifiées. Finalement, on devra régler la question de la chirurgie conservatrice comme traitement acceptable du cancer du sein; autrement, l'intervention prophylactique est possiblement plus invasive et mutilante que le traitement de la maladie qu'elle cherche à prévenir.

From the Department of Health Care and Epidemiology, Faculty of Medicine, University of British Columbia, Vancouver, BC

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

Accepted for publication Jan. 7, 1985

Reprint requests to: Dr. Martin T. Schechter, Department of Health Care and Epidemiology, University of British Columbia, Mather Building, 5804 Fairfield Ave., Vancouver, BC V6T 1W5

There are several different aspects to the selection of women who are at high risk for breast cancer. One question is which women are at highest risk? It is perhaps on these women that preventive and health-promotion measures could be concentrated for optimum results.

A second question pertains to issues in screening; which women are the most

likely to have a breast cancer detected on screening? If a strategy for identifying such women was available, then the resources for screening as well as the hazards of annual mammography could be concentrated only on the identified subgroup of women at high risk. This would make better use of resources, lower the screening-related risk and, most important, annual screening would be more widely accepted by healthy women and physicians.

Finally, a third related question is raised by this symposium. Which of the women with certain "precancerous" lesions are at highest risk of subsequently having invasive carcinoma? Can we accurately estimate the risk in individual patients so as to guide our management better? Clearly, accurate estimates of risk are necessary if we are to make intelligent decisions regarding the use of such procedures as prophylactic mastectomy.

For purposes of review, let us recall some of the characteristics necessary for successful surgical prophylactic procedures, such as prophylactic mastectomy or colectomy. First, the prophylactic maneuver should effectively prevent the disease. Second, the population at high risk should be easily identifiable. Third, the benefit of the prophylactic maneuver should outweigh its cost in this high-risk population.

Here, benefit and cost should be viewed in their wider sense. Benefit refers to both financial and health benefits, including any morbidity and mortality avoided by prophylaxis, while costs refer to both financial and health cost, including any morbidity and mortality, anxiety, labelling effects, and so on, caused by the maneuver.

Clearly, the more successful we are at identifying the high-risk population, the more likely it is that the cost-benefit equation will be satisfied. This can be seen most readily by the radical proposal that all women undergo prophylactic mastectomy at the age of 30 years. This would do wonders for breast cancer mortality in our society but clearly cost would far outweigh benefit.

It is also critical to remember that it is the psychological and emotional profile of the individual woman that decides the utilities that are to be assigned to the various management options. There are patients who, for various reasons, will choose to avoid mastectomy at all costs no matter what the risk of subsequent cancer is, while others find greater benefit in eliminating the continuous anxiety and fear associated with repeated biopsies.

Selection

With regard to selection strategies, I would like to make three key points. First, I would emphasize that the etiology of breast cancer is exceptionally complex, representing a poorly understood interplay of reproductive, hormonal, genetic and environmental factors. Second, most risk factors have modest etiologic force; that is, their relative risks are modest, in the neighbourhood of two to five times the normal, and it is their combination that determines overall risk. Haagensen[1] called this the "cumulative predisposition". Unlike cigarette smoking and its relation to lung cancer, there is no individual risk factor for breast cancer that is so highly culpable. Third, simplistic approaches to selecting women at high risk will not suffice; that is, simple approaches to risk-factor information will provide only simple answers and, given the complexity of breast cancer, these will probably not be satisfactory.

Family History

An excellent example of the insight gained from a more complex analysis concerns the question of family history. Consider the example of a 31-year-old woman whose mother and three maternal aunts all have breast cancer. The question of prophylactic mastectomy is raised. To begin with, the overall cumulative lifetime risk for the average 31-year-old woman has been estimated to be about 7% to 8%.[2] The simple approach in the past in considering family history has been to assign an overall relative risk, usually around two, to women with a family history of breast cancer. The cumulative lifetime risk would therefore be around 15% for such a woman. If we add some complexity, however, we find that the risk differs if the familial cancer was unilateral or bilateral and if it occurred before or after the menopause (Table I).[3] If the familial cancer is premenopausal and bilateral, the relative risk is estimated to be almost nine and the cumulative risk is 45%. On the other hand, if the familial cancer is postmenopausal and unilateral, which represents most familial cancers, there is virtually no increase in risk at all. The same holds true for multiple familial cancer. If two sisters have premenopausal bilateral breast cancer, the cumulative risk for another sister is estimated to be about 50%. But if the sisters both have postmenopausal, unilateral disease, there is again virtually no increase in risk.

Returning to our example, we find that all of our patient's familial cancers were in fact unilateral and postmenopausal. From these data, she appears to be at very little, if any, increased risk of breast cancer. This is so despite what appears to be at first glance an extremely strong family history.

What has occurred here is that a risk factor, in this case family history, has been found to interact with menopausal status and laterality. As a result, instead of implicating family history to a mild degree in all women with family histories, the risk can be concentrated on the extremely small number of women with familial histories of premenopausal, bilateral disease, and the majority of

Table I—Risk to First-Degree Relative by Menopausal Status and Laterality of Familial Cancer*

Time	Unilateral	Bilateral
Premenopause	1.8† (10%‡)	8.8 (45%)
Postmenopause	1.2 (7%)	4.0 (20%)

*Adapted from Kelly PT and Anderson DE.[3]
†Relative risk.
‡Cumulative risk.

Table II—Risk Factors for Breast Cancer in Women

	Risk		
Factor	High	Low	Relative risk
Age	Old age	Young age	> 4.0
Age at first birth	> 30 yr	< 20 yr	2.0–4.0
Oophorectomy	No	Yes	2.0–4.0
Body build	Obese	Thin	2.0–4.0
Age at menarche	Early	Late	1.1–1.9
Age at menopause	Late	Early	1.1–1.9
Family history of premenopausal bilateral breast cancer	Yes	No	> 4.0
History of cancer in one breast	Yes	No	> 4.0
History of fibrocystic disease	Yes	No	2.0–4.0
Any first-degree relative with breast cancer	Yes	No	2.0–4.0
History of primary cancer in ovary or endometrium	Yes	No	2.0–4.0
Radiation to chest	Large doses	Minimal exposure	2.0–4.0

*Adapted from Kelsey JL.[4]

women with family histories, that is those with familial histories of postmenopausal unilateral disease, are exonerated.

Risk Factors

There seem to be many risk factors for breast cancer: increasing age, premenopausal bilateral breast cancer in a first-degree relative, a history of breast cancer in the contralateral breast and certain precancerous or high-risk lesions are associated with the largest relative risks. Late age at first live birth, early age at menarche, late age at menopause, a history of fibrocystic disease, low parity, radiation to the chest and obesity have also been implicated (Table II[4]). In addition, there are the emerging questions surrounding the role of dietary fat consumption, the possible role of smoking and a possible positive effect of long-term use of oral contraceptives in young women.

On another level, various pathological diagnoses may be predictors. With regard to fibrocystic disease, the specific diagnoses that are thought to be associated with subsequent breast cancer are atypical epithelial hyperplasia, atypical lobular hyperplasia and diffuse papillomatosis with atypia. However, it is important to point out that the elevated risks associated with these diagnoses have not been demonstrated consistently and that if such elevations exist, they are likely only to be in the neighbourhood of a two- to fourfold increase. Clearly, this would not justify a consideration of prophylactic mastectomy.

High-Risk Lesions

To approach the question of high-risk lesions, consider the example of a 42-year-old premenopausal woman with three children, whose first child was born when she was 21 years of age, whose menarche was at 14 years and who has just had lobular carcinoma in situ found on breast biopsy. Clearly, the question of management for this patient depends on the underlying question of whether invasive breast cancer will develop. We know that this woman has a high-risk lesion and carries an increased risk of breast cancer developing, but exactly how high is this risk?

Data from past studies[5] suggest she has about a 35% chance of having invasive cancer within 20 years. Is the increase in risk from 7% to 35% sufficient cause to consider prophylactic mastectomy in this patient? This study[5] was retrospective so that there are problems with the cohort of women assembled for follow-up. For example, the age ranged from 27 to 55 years so it is difficult to know how to apply the results to any given age group. The most glaring deficiency is that only 50 patients were considered in this study. The use of such small numbers results in a lack of statistical precision. The key estimate of 35%, for example, was based on only nine cases. In this study, 31 women were lost to follow-up so that after 10 years, only 15 women were being followed up. If one were to put 95% confidence limits around the estimates, one would obtain a range of from 12% to 57% for the average 20-year risk of invasive carcinoma. The lower end of this range is not much higher than the 8% cumulative risk applicable to the general population. The results are further confounded by the fact that in 45 of the 50 women biopsies were done because of the clinical presence of fibrocystic disease. Many of these criticisms hold as well for most other studies in this area. Furthermore, we have no data on the influence of other risk factors such as age at first live birth, age at menarche, and so on, and how these risks might be modified. These data certainly suggest that women with lobular carcinoma in situ are at elevated risk for invasive breast cancer, but precise estimates of how high the risk is are lacking. However, ongoing clinical trials of breast cancer screening and of breast cancer therapies may provide more sound estimates in the future.

If we accept these estimates, then of 100 women like our patient, 35 or so will suffer invasive cancer within 20 years. Just as a half-full glass is also half-empty, it is important to note that 65 of those women will not have invasive carcinoma. These constitute a fascinating group of women who have a known precursor and yet, perhaps for hormonal, dietary, reproductive or genetic reasons, invasive disease does not develop. An analysis of the factors that protect these women could be important to our understanding of breast cancer etiology.

Even among the unfortunate women with lobular carcinoma in situ who subsequently have invasive cancer, the evidence suggests that the invasive cancer is just as likely to occur in the contralateral as in the ipsilateral breast. Moreover, the invasive cancer that develops is more likely to be intraductal than lobular and is unlikely to be in the same site as the original lesion. These facts suggest that the hypothesis that the lobular carcinoma in situ progresses in a stepwise fashion to become the invasive cancer, is untenable. More reasonable is the hypothesis that lobular carcinoma in situ is a marker for women at high risk, in much the same way as a history of premenopausal bilateral breast cancer in a first-degree relative is.

Conclusions

Lobular Carcinoma in Situ

From these observations, there appear to be some logical conclusions. First, since both breasts are at equal risk, the management of the contralateral breast should be identical to that of the ipsilateral one. Second, since lobular carcinoma in situ should be viewed as a risk factor or marker and not as a precursor, any management policy for this lesion should be applied as well to any risk factor of equal magnitude, such as premenopausal bilateral breast cancer in a first-degree relative. Since the risk of subsequent invasive cancer in women with such a family history has been estimated to be approximately of the same magnitude as the risk for women with lobular carcinoma in situ, then the management policy for each of these situations should be the same.

Does it logically follow from this that a policy of bilateral mastectomy is justified for lobular carcinoma in situ or any other risk factor of equal magnitude? Given the paucity of data and our current inability accurately to assess risk, I do not believe that such a policy can be justified.

Intraductal Carcinoma

The situation with regard to intraductal carcinoma may be clearer. This is not because the estimates of risk are any sounder than for lobular carcinoma in situ, since again the numbers of patients followed in studies are woefully inadequate. What is clearer is the observation that subsequent invasive cancer, when it occurs, tends to do so in the ipsilateral breast only and the histologic type of the subsequent cancer is usually ductal. These observations support the hypothesis that intraductal carcinoma is a precursor lesion with malignant potential. For these reasons, prophylactic mastectomy has been far less controversial as treatment for intraductal carcinoma than it has been for lobular carcinoma in situ. However, it is important to note that our knowledge of the true risk associated with intraductal lesions is imprecise. The methodologic problems cited earlier apply also to the follow-up studies of women with this type of lesion. There is evidence to suggest that in a significant proportion of women with intraductal cancer, the disease does not progress to invasive cancer.[6]

Prophylactic Mastectomy

Policies concerning prophylactic mastectomy become even more difficult in the light of recent changes in our attitude concerning the primary therapy of breast cancer. If the recent trend towards more breast-conserving surgery such as lumpectomy continues, it may very well violate the cost-benefit equation to advocate a prophylactic procedure that is far more aggressive and disfiguring than the eventual therapy of the disease that the

prophylactic procedure seeks to prevent.

The only way prophylactic mastectomy might be applied rationally is if more exact estimates of risk of subsequent invasive cancer in women with these lesions were available and if methods were developed for identifying those women with such lesions who are at exceptionally high risk. Such methods are not yet available. The National Breast Screening Study of Canada,[7] a randomized controlled trial currently being conducted across Canada, is recruiting 90 000 women to assess the benefits of annual screening. Using data from this study and a multivariate biostatistical technique known as logistic discriminant analysis, we were able to combine risk factors such as age at first live birth and family history, to discern women at high risk. These methods allowed us to identify 40% of the population in whom 85% of all breast cancers occur. It is hoped that prospective data arising from this study as well as from ongoing clinical trials of breast cancer therapy will provide more accurate estimates of risk for women with high-risk lesions and similar discriminants to identify women at exceptionally high risk for whom prophylactic procedures may be warranted. Such discriminants may be complex, combining the risk-factor information and histopathologic features of the original lesion. It is conceivable that methods will exist for selecting out of all women with lobular carcinoma in situ, 40% to 50% in whom most of the invasive cancers will occur. The cumulative risk in such women might approach 70% or beyond so that a prophylactic intervention could be more easily justified. Moreover, it would reduce the number of women considered for prophylaxis by 50% or more. Until these methods exist, however, and until the question of breast conservation as an acceptable therapy for invasive cancer is settled, I do not believe there is sound epidemiologic evidence to support an overall policy of prophylactic mastectomy.

References

1. HAAGENSEN CD: *Diseases of the Breast*, 2nd ed, Saunders, Philadelphia, 1971
2. SILVERBERG E: Cancer statistics, 1983. *CA* 1983; 33: 9–25
3. KELLY PT, ANDERSON DE: Familial breast cancer. In: *Your Patient and Cancer*, vol. 1, Dominus Pub, Lincoln, Neb., 1981: 25
4. KELSEY JL: A review of the epidemiology of human breast cancer. *Epidemiol Rev* 1979; 1: 74–109
5. MCDIVITT RW, HUTTER RV, FOOTE FW JR, STEWART FW: In situ lobular carcinoma. A prospective follow-up study indicating cumulative patient risks. *JAMA* 1967; 201: 82–6
6. PAGE DL, VANDER ZWAAG R, ROGERS LW, WILLIAMS LT, WALKER WE, HARTMANN WH: Relation between component parts of fibrocystic disease complex and breast cancer. *JNCI* 1978; 61: 1055–63
7. MILLER AB, HOWE GR, WALL C: The National Study of Breast Cancer Screening Protocol for a Canadian randomized controlled trial of screening for breast cancer in women. *Clin Invest Med* 1981; 4: 227–58

LOUIS R. BÉGIN, MD, FRCPC

2. Definition of Precancerous and High-Risk Mammary Lesions

Intraepithelial (noninvasive) neoplasia of breast, the most potent precursor of invasive carcinoma, comprises two types: lobular carcinoma in situ and ductal carcinoma in situ. Their respective morphologic character, biologic significance and natural history are discussed. Borderline lesions, such as atypical lobular hyperplasia and atypical ductal hyperplasia, are defined and their importance as risk factors for subsequent carcinoma is emphasized. Analysis of the concept of fibrocystic disease recognizes a lack of both pathologic specificity and predictive value as a risk factor for malignant disease. Rather than referring to fibrocystic disease, this complex should be stratified in specific histologic types to understand better its biologic significance.

Les néoplasies intraépithéliales (non invasives) du sein, qui représentent les plus sérieux précurseurs d'un carcinome invasif, sont de deux types: les carcinomes lobulaires in situ et les carcinomes canaliculaires in situ. On commente leurs caractères morphologiques respectifs, leur importance biolologique et leur histoire naturelle. Les cas limites, tels que l'hyperplasie lobulaire atypique et l'hyperplasie canaliculaire atypique, sont définis, et leur importance en tant que facteur de risque d'un cancer subséquent est soulignée. À l'analyse, le concept de maladie fibrokystique du sein n'offre ni spécificité pathologique, ni valeur prévisionnelle comme facteur de risque. Plutôt que d'en référer à la maladie fibrokystique, il vaudrait mieux stratifier les cas d'après le type histologique spécifique afin de mieux comprendre l'importance biologique de celui-ci.

From the Department of Pathology, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, PQ

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

Accepted for publication Jan. 7, 1985

Reprint requests to: Dr. L.R. Bégin, Assistant Professor of Pathology, Sir Mortimer B. Davis–Jewish General Hospital, 3755 Côte Ste-Catherine, Montreal, PQ H3T 1E2

It is well established that lobular carcinoma in situ and ductal carcinoma in situ (intraductal carcinoma) are the most significant and potent precursors of invasive breast cancer. Their distinctive natural history has been elucidated through recent retrospective studies.[1-4] Both lesions have been legitimately included in the concept of minimal breast cancer.

Lobular Carcinoma in Situ

Lobular carcinoma in situ represents 28% to 37%[5,6] of all cases of carcinoma in situ. It is defined as involvement of a variable number of terminal lobular units by a proliferation of monotonous cells that obliterate luminal spaces, with a variable degree of distension (Fig. 1). It is usually an incidental finding on histologic examination of a biopsy specimen for such conditions as fibrocystic disease. A high degree of alertness and adequate fixation of tissue are prerequisites for histologic recognition. Noninvasion is assumed on the basis of insular groups of cells with a smooth and spherical contour, centred around the terminal ductule. There are two cytologic subtypes, which may be combined. The first is characterized by a monotonous population of polygonal cells with a pale or amphophilic cytoplasm. Intracytoplasmic globules or lumina are frequently noted.[7] Nuclei are round, with little variation in size; they often display a finely dispersed chromatin with inconspicuous nucleoli. Mitoses are sparse or absent. The second subtype is characterized by a population of more pleomorphic, less-cohesive cells with anisocytosis that may display prominent nucleoli. These two subtypes have been designated types A and B respectively by Haagensen and colleagues.[8] Retrograde ductal involvement is not unusual; tumour cells may be insinuated between the basement membrane, with or without

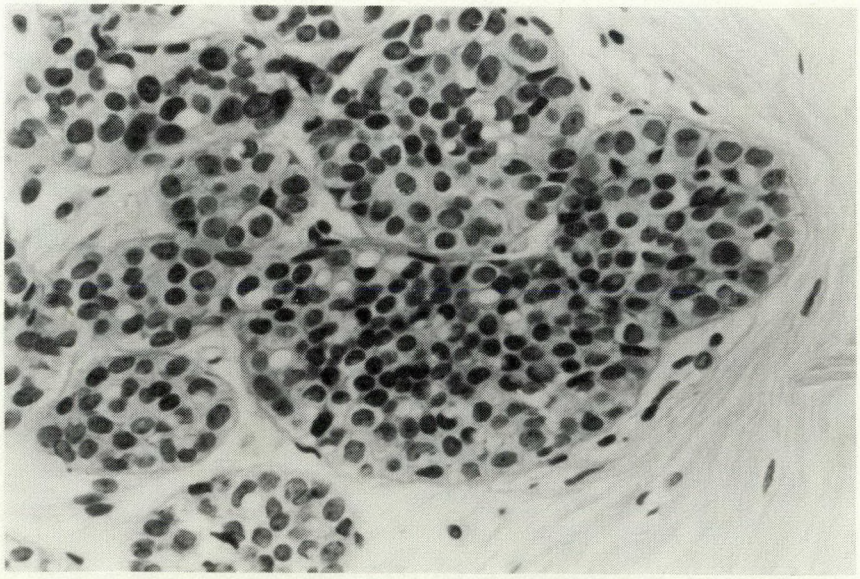


FIG. 1—Lobular carcinoma in situ. Distension of terminal lobular unit by solid population of monotonous cells. Note frequent intracytoplasmic, clear globules (hematoxylin and eosin, × 400).

outer budding and preservation of inner lining epithelium.[9,10] The pathologist should not confuse this pattern with ductal carcinoma in situ (the clinging pattern), a disease of distinct biologic significance. The retrograde extension of lobular carcinoma in situ has been referred to as Pagetoid spread.[9] On the other hand, it is important to distinguish between lobular carcinoma in situ and intraductal carcinoma within the lobular unit, since the latter may extend centrifugally and involve the terminal lobular unit. This process has been termed lobular canceration.[9] Occasionally, this phenomenon is the only detectable topographic histologic pattern. A cribriform pattern, a more pleomorphic tumour cell population and cell necrosis are more likely to indicate lobular canceration (Fig. 2).

The retrospective study of Rosen and colleagues[1] has elucidated the biology of lobular carcinoma in situ. They analysed 84 patients, treated by biopsy only and followed up for an average of 24 years. Subsequent invasive carcinoma developed in 28 (33%) of the patients, in the ipsilateral breast in 12, in the contralateral breast in 9 and in both breasts in 7. In regard to histiotype, there were 20 invasive ductal carcinomas, 13 invasive lobular, 1 mucinous and 1 tubular carcinoma. Interestingly, the majority of subsequent carcinomas became evident 15 or more years after the original biopsy and 38% were not detected until 20 years later.[1] Still unexplained is why, although 60% of subsequently studied mastectomy specimens harboured foci of residual lobular carcinoma in situ, less than half of the patients treated by biopsy only would subsequently have ipsilateral carcinoma.[11] These findings suggest that lobular carcinoma in situ is a tissue marker for increased risk of subsequent invasive carcinoma of any histiotype, in the whole bilateral mammary parenchyma. Lobular carcinoma in situ is a potent, anatomically defined risk factor for subsequent invasive carcinoma, carrying a ninefold relative risk for the patient.[1]

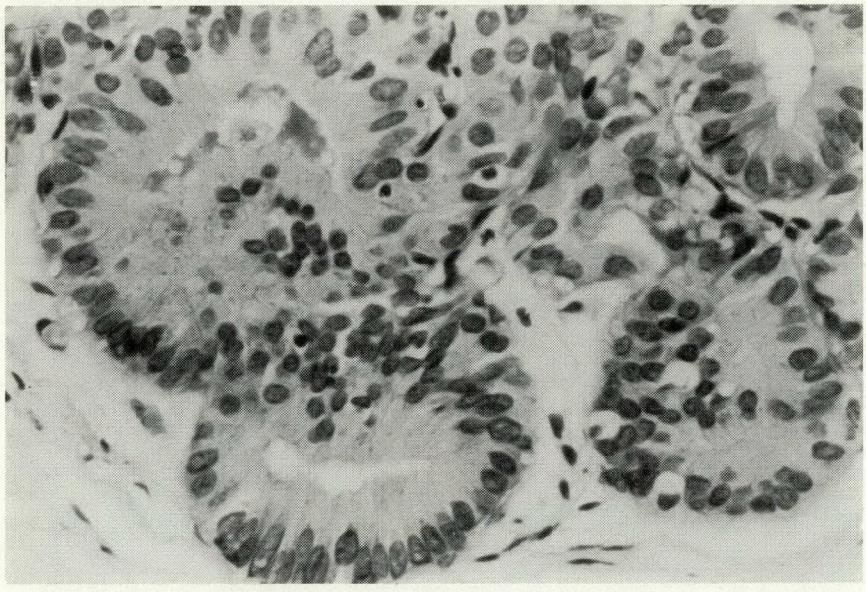


FIG. 2—Lobular canceration by ductal carcinoma in situ. Lobular unit displays malignant columnar cells surrounding well-formed holes. This should be distinguished from lobular carcinoma in situ (hematoxylin and eosin, × 400).

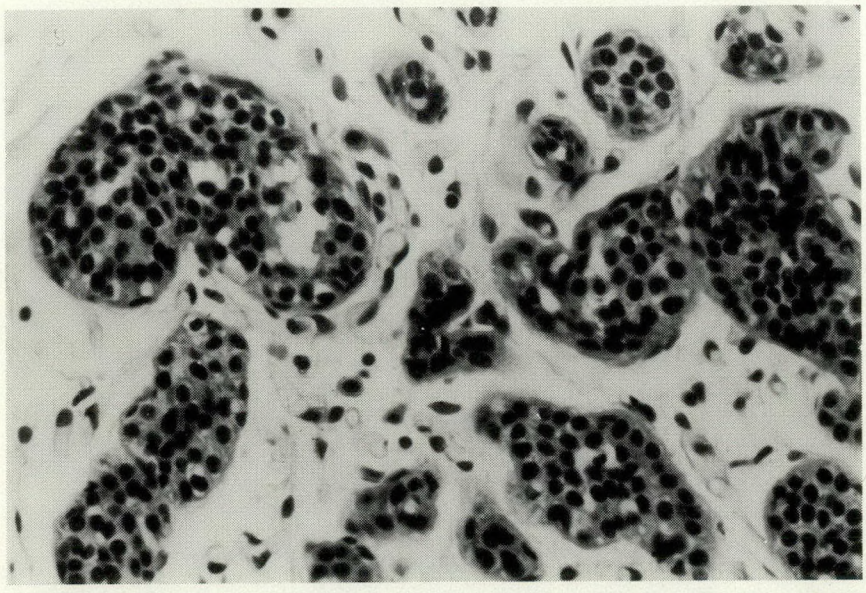


FIG. 3—Atypical lobular hyperplasia. Proliferation of monotonous cells without significant lobular distension. Residual luminal spaces are present (hematoxylin and eosin, × 400).

Atypical Lobular Hyperplasia

Atypical lobular hyperplasia is best defined as a histologic entity that does not fulfil all the criteria for the definition of lobular carcinoma in situ. There is no detectable distension of the lobular unit and residual lumina are present (Fig. 3). Nuclei may appear partly ovoid and overlap.[9] It has been suggested that this lesion could represent the "early" or incomplete form of lobular carcinoma in situ.[12] Recent studies have defined the relative risk.[13,14] A retrospective analysis of 125 cases of atypical lobular hyperplasia revealed that in 14% of these patients invasive carcinoma developed, representing a relative risk of 4.4, in contrast to the relative risk of 9 for lobular carcinoma in situ.[14]

Intraductal Carcinoma

Intraductal carcinoma has a distinctive biologic and histologic character. Clinically, it appears as a discrete or questionable mass in about 75% of cases.[15] Symptoms are also more likely before invasion occurs if the lesion is central and subareolar. A minimal tumour sampling of 6 to 10 blocks has been suggested as basic requirement to rule out invasion.[16,17] It is most important to ensure a diagnosis of pure (noninvasive) intraductal carcinoma if the surgeon is not going to perform a nodal dissection. Intraductal proliferation of malignant cells depicting a solid, papillary or cribriform pattern of growth is characteristic (Fig. 4). Tumour cells are usually more pleomorphic than those found in lobular carcinoma in situ and necrosis, referred to as comedo-type, is frequently observed. The histologic judgement of noninvasion is based on a spherical ductal contour and sharp epithelial–stromal demarcation. An associated inflammatory cell response may be present. In spite of the absence of demonstrable stromal invasion, on rare occasions nodal metastasis may occur. This could be explained on the basis of inadequate tumour sampling or early escape of tumour cells from the basal lamina. Indeed, Ozzello[18] demonstrated transgression of basal lamina by tumour

cells at the ultrastructural level. Intraductal carcinoma may occasionally depict the so-called clinging pattern, defined as one or a few layers of malignant cells lining the ductal system.[9] The diagnosis often depends on the alertness of the pathologist and may easily be missed. Extension to lobular unit (lobular canceration) or epidermotropism (Paget's disease) are also possible pertinent findings on pathological examination.

The natural history of intraductal carcinoma has been described in two major series in which patients were treated by biopsy only.[3,4] In a series of 15 patients, 7 had ipsilateral invasive carcinoma within 10 years.[4] In a second series of 28 patients, with average follow-up of 16 years, 7 patients had ipsilateral invasive carcinoma within an average of 6 years. In none of these patients did cancer develop contralaterally and the invasive ductal carcinoma was of the conventional ductal histiotype.[3] Although the overall risk for subsequent invasive carcinoma is similar to that for lobular carcinoma in situ, the ipsilateral localization and much shorter interval to the development of invasive cancer are quite distinct.

Fibrocystic Disease Complex

Fibrocystic disease as a risk factor for breast carcinoma is of dubious significance. The main reason is that this lesion embraces a spectrum of hormonal, stromal and epithelial changes. Indeed, numerous histopathologic findings are included in this complex. It has been suggested that the term fibrocystic disease be characterized by more specific histologic determinants in order to allow a better histologic classification and prospective analysis.[19] Historically, it has been estimated that fibrocystic disease carries a risk factor of no more than 1.5 to 2.5.[9] We have characterized the fibrocystic disease complex into specific histologic categories (Table I). That without epithelial hyperplasia is characterized by cysts, fibrosis and apocrine metaplasia. No significant risk for cancer development has been convincingly demonstrated. Fibrocystic disease with epithelial hyperplasia (intraductal or intraductular hyperplasia, or both, and epitheliosis) is characterized by a multicentric, benign proliferation of both epithelial and

Table I—Fibrocystic Disease Complex of the Breast

Without epithelial hyperplasia
With epithelial hyperplasia
Not otherwise specified
Atypical
Radial scar
Blunt duct and sclerosing adenosis

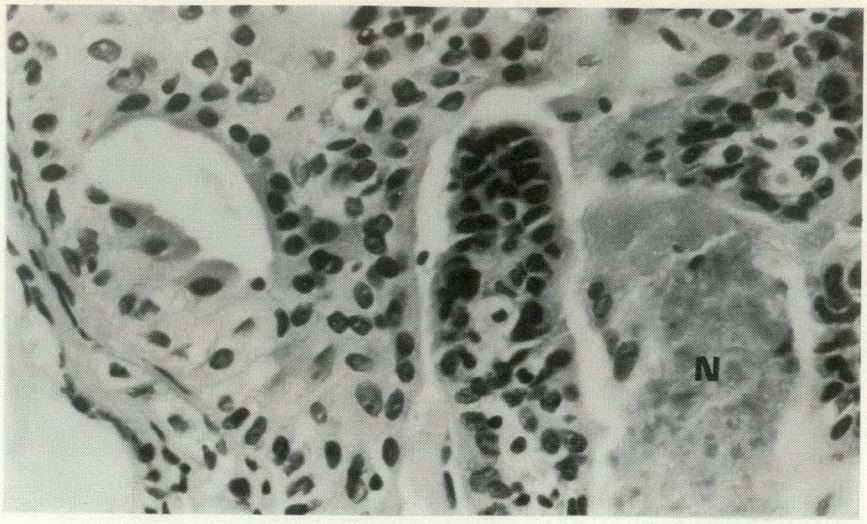


FIG. 4—Intraductal carcinoma. Intraductal proliferation of polygonal cells, displaying hyperchromasia, solid papillary tufting and necrosis (N) (hematoxylin and eosin, × 400).

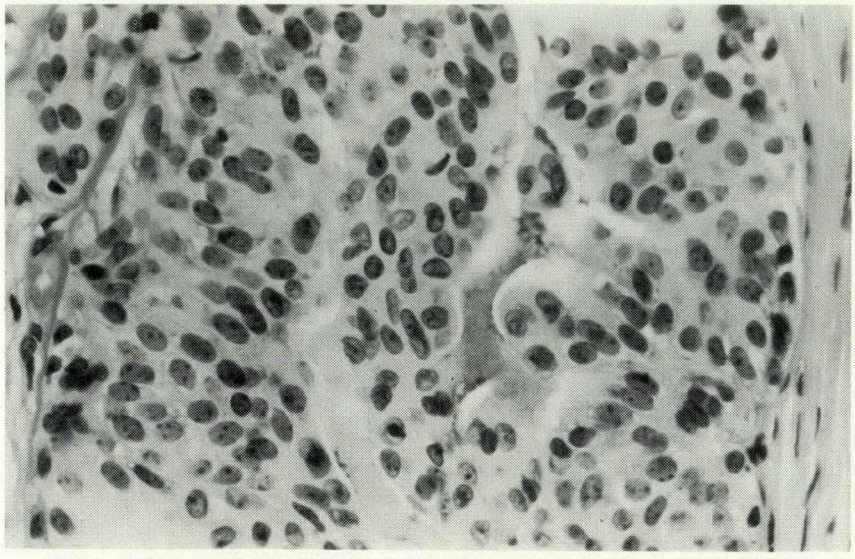


FIG. 5—Atypical ductal hyperplasia. Proliferation of monotonous cells with variable nuclear hyperchromasia and without distinct myoepithelial differentiation. Irregular luminal spaces are present. This represents minimal deviation from lobular carcinoma in situ (hematoxylin and eosin, × 400).

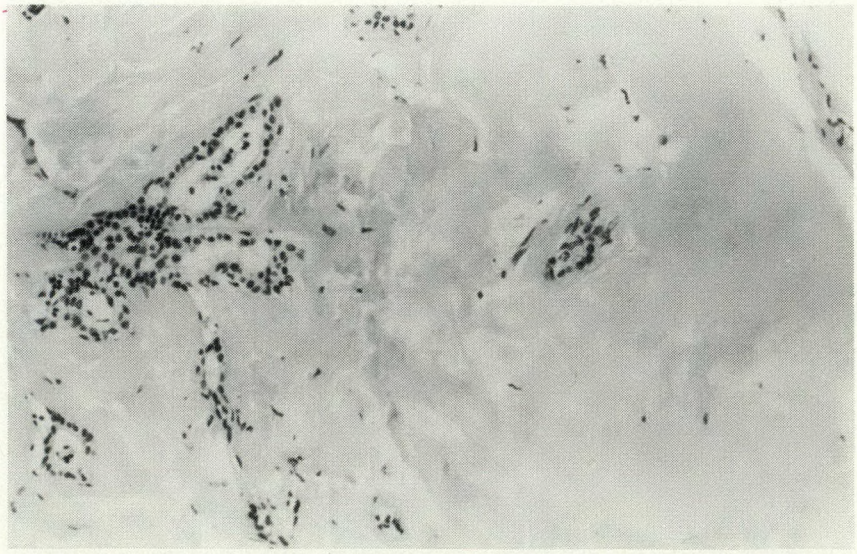


FIG. 6—Radial scar. Presence of fibroelastotic scar (right side) with radiating tubular structures (left side) (hematoxylin and eosin, × 160).

myoepithelial cells. Most important in this category is the recognition of the atypical form of epithelial hyperplasia, referred to as atypical ductal hyperplasia. This condition is defined as a lesion displaying cytoarchitectural features in the borderline zone between not-otherwise-specified epithelial hyperplasia and intraductal carcinoma (Fig. 5). The histologic deviation from intraductal carcinoma may be minimal and in some cases clear distinction is not feasible. The lesion may meet some but not all of the criteria for intraductal carcinoma.[20] For example, luminal spaces are not clearly slit-like or hole-like, the cell population is often monotonous and nuclear hyperchromasia is inconstant. A recent retrospective analysis of 149 such cases showed a 12% incidence of subsequent invasive carcinoma and a relative risk factor of 4.2.[14] In fact, this risk is not substantially different from that for atypical lobular hyperplasia.[14] The overall risk for atypical proliferative lesions is about one half of that for carcinomas in situ but comes close to it if there is a positive family history.[14] If the atypical group of proliferative lesions is excluded, there is no convincing evidence that blunt duct, sclerosing adenosis and fibrocystic disease complex without hyperplasia are important risk factors.

Radial scar is a lesion that has received close attention from pathologists lately. It is likely to be misinterpreted as a malignant lesion on both radiologic[21] and pathologic examination. Of unknown etiology, the lesion measures from 3 to 16 mm in size and is frequently multicentric.[22,23] It is characterized by a central, fibroelastotic core from which radiate tubular structures, with or without papillary proliferation (Fig. 6). A complex pathologic nomenclature has been used to describe this entity,[22] but radial scar is the simplest descriptive term. Postulated to represent an early incipient tubular carcinoma,[24] no convincing demonstration has been made. Its biologic significance as a histologic risk factor for cancer is controversial. In a retrospective study of 32 cases with a mean follow-up of 19.5 years, only one patient subsequently had ipsilateral invasive carcinoma. This is not significantly different from the expectation in normal control subjects.[22] On the other hand, an autopsy study showed a higher incidence and greater number of radial scars in cancer-associated mammary parenchyma than in breast presumed to be at low risk for development of cancer.[23] The latter findings suggest that radial scar carries a risk factor for cancer development.

Although lobular and ductal carcinomas in situ are well understood in regard to their pathological definition and natural history, we await the emergence of new studies that should clarify the biologic significance of fibrocystic disease. Histologic stratification in such a complex entity appears essential to delineate precise diagnostic criteria and for an understanding of biologic data.

References

1. ROSEN PP, KOSLOFF C, LIEBERMAN PH, ADAIR F, BRAUN DW JR: Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. *Am J Surg Pathol* 1978; 2: 225–51
2. ROSEN PP, BRAUN DW JR, KINNE DE: The clinical significance of pre-invasive breast carcinoma. *Cancer* 1980; 46(4 suppl): 919-25
3. PAGE DL, DUPONT WD, ROGERS LW, LANDENBERGER M: Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer* 1982; 49: 751–8
4. BETSILL WL JR, ROSEN PP, LIEBERMAN PH, ROBBINS GF: Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. *JAMA* 1977; 239: 1863–7
5. BEDWANI R, VANA J, ROSNER D, SCHMITZ RL, MURPHY GP: Management and survival of female patients with "minimal" breast cancer: as observed in the long-term and short-term surveys of the American College of Surgeons. *Cancer* 1981; 47: 2769–78
6. SMART CR, MYERS MH, GLOECKLER LA: Implications from SEER data on breast cancer management. *Cancer* 1978; 41: 787–9
7. ANDERSEN JA, VENDELBOE ML: Cytoplasmic mucous globules in lobular carcinoma in situ. Diagnosis and prognosis. *Am J Surg Pathol* 1981; 5: 251–5
8. HAAGENSEN CD, LANE N, LATTES R: Neoplastic proliferation of the epithelium of the mammary lobules: adenosis, lobular neoplasia, and small cell carcinoma. *Surg Clin North Am* 1972; 52: 497–524
9. AZZOPARDI JG: *Problems in Breast Pathology,* Saunders, Philadelphia, 1979
10. HAAGENSEN CD, LANE N, LATTES R, BODIAN C: Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer* 1978; 42: 737–69
11. ANDERSEN JA: Lobular carcinoma in situ. A long-term follow-up in 52 cases. *Acta Pathol Microbiol Scand [A]* 1974; 82: 519–33
12. WELLINGS SR, JENSEN HM, MARCUM RG: An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. *J Natl Cancer Inst* 1975; 55: 231–73
13. PAGE DL, VANDER ZWAAG R, ROGERS LW, WILLIAMS LT, WALKER WE, HARTMANN WH: Relation between component parts of fibrocystic disease complex and breast cancer. *JNCI* 1978; 61: 1055–63
14. PAGE DL, DUPONT WD, ROGERS LW: Atypical hyperplasia of the breast (abstr). *Lab Invest* 1984; 50: 44
15. WESTBROOK KC, GALLAGER HS: Intraductal carcinoma of the breast. A comparative study. *Am J Surg* 1975; 130: 667–70
16. MCDIVITT RW, STEWART FW, BERG JW: *Tumors of the Breast,* Armed Forces Institute of Pathology, Washington, DC, 1968
17. SILVERBERG SG, CHITALE AR: Assessment of significance of proportions of intraductal and infiltrating tumor growth in ductal carcinoma of the breast. *Cancer* 1973; 32: 830–7
18. OZZELLO L: The behavior of basement membranes in intraductal carcinoma of the breast. *Am J Pathol* 1959; 35: 887–99
19. LOVE SM, GELMAN RS, SILEN W: Fibrocystic "disease" of the breast — a nondisease? *N Engl J Med* 1982; 307: 1010–4
20. ASHIKARI R, HUVOS AG, SNYDER RE, LUCAS JC, HUTTER RV, MCDIVITT RW, SCHOTTENFELD D: Proceedings: a clinicopathologic study of atypical lesions of the breast. *Cancer* 1974; 33: 310–7
21. KEEN M, MATTHIES H, MURAD T: Benign breast lesions with malignant clinical and mammographic presentations (abstr). *Lab Invest* 1984; 50: 30
22. ANDERSEN JA, GRAM JB: Radial scar in the female breast. A long-term follow-up study of 32 cases. *Cancer* 1984; 53: 2557–60
23. WELLINGS SR, ALPERS CE: Subgross pathologic features and incidence of radial scars in the breast. *Hum Pathol* 1984; 15: 475–9
24. FISHER ER, PALEKAR AS, KOTWAL N, LIPANA N: A nonencapsulated sclerosing lesion of the breast. *Am J Clin Pathol* 1979; 71: 240–6

NORMAN WOLMARK, MD, FRCSC, FACS

3. Minimal Breast Cancer: Advance or Anachronism?

The author argues that minimal breast cancer does not represent a distinct disease entity but comprises three discrete components, each with unique characteristics. The natural history of lobular carcinoma in situ and intraductal cancer, two of the components of minimal breast cancer, is described. The dangers of relying on a data base established on the strength of retrospective anecdotal information is underscored. Lobular carcinoma in situ has a propensity for multicentricity and bilaterality. In 25% of patients with lobular carcinoma in situ, invasive breast cancer will develop subsequently, and the majority of these tumours will be of ductal origin. The average interval from the diagnosis of lobular carcinoma in situ to the development of subsequent invasive cancer is over 15 years and both breasts are at equal risk. Based on this information, the use of bilateral prophylactic mastectomy is unjustified. In contrast to lobular carcinoma in situ, 25% to 50% of patients with intraductal carcinoma will subsequently have infiltrating cancer, at an average of 10 years after the initial biopsy. Although the putative incidence of multicentricity is 50%, virtually all subsequent invasive cancers occur not only in the same breast but in the same quadrant as the initial lesion. In light of the momentum for breast-preserving operations in invasive cancer, clinical trials should be implemented to assess the propriety of conservative management with and without radiotherapy in patients with intraductal carcinoma.

L'auteur argumente que le cancer circonscrit du sein n'est pas une entité distincte mais qu'il comprend plutôt trois composantes discrètes ayant chacune des caractéristiques uniques. L'histoire naturelle du cancer lobulaire in situ et du cancer intracanaliculaire, deux des composantes du cancer circonscrit du sein, est décrite. On souligne les dangers de se fier à des données reposant sur des informations anecdotiques rétrospectives. Le cancer lobulaire in situ a tendance à devenir multicentrique et bilatéral. Dans 25% des cas de cancer lobulaire in situ, un cancer invasif du sein se développe subséquemment, et la majorité de ces tumeurs prendra naissance dans les canaux galactophores. L'intervalle moyen entre le diagnostic de cancer lobulaire in situ et l'apparition d'un cancer invasif est de plus de 15 ans et chacun des seins est également menacé. A partir de ceci, on ne peut justifier le recours à la mastectomie bilatérale prophylactique. A l'opposé du cancer lobulaire in situ, 25% à 50% des patientes atteintes de cancer intracanaliculaire développeront un cancer infiltrant dans les 10 années qui suivront la biopsie initiale. Bien que l'incidence putative des cancers multicentriques soit de 50%, pratiquement tous les cancers envahissants subséquents apparaissent non seulement dans le même sein mais, encore, dans le quadrant qui avait été soumis à la biopsie initiale. Devant la popularité actuelle des opérations visant à préserver le sein dans les cas de cancers envahissants, il y aurait lieu de mettre sur pied des essais cliniques destinés à évaluer la justesse d'un traitement conservateur avec ou sans radiothérapie chez les patientes souffrant de cancer intracanaliculaire.

From the Department of Surgery, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

Accepted for publication Jan. 7, 1985

Reprint requests to: Dr. N. Wolmark, Department of Surgery, School of Medicine, University of Pittsburgh, 3459 Fifth Avenue, Pittsburgh, PA 15213, USA

The formulation and adoption of new cancer terminology is associated with an inherent obligation — that the new definition describes a meaningful clinical entity, the study of which furthers the biologic understanding of the disease process in question. These prerequisites are not fulfilled by the term "minimal breast cancer". This definition was introduced in 1971 by Gallager and Martin[1] to describe "breast carcinoma that is readily curable by available means". They characterized minimal breast cancer as comprising three distinct processes: (a) lobular carcinoma in situ, (b) noninvasive intraductal carcinoma and (c) invasive adenocarcinoma having a maximum diameter of 0.5 cm. They selected 0.5 cm as the upper limit for compliance from their hypothetical estimation that the incidence of nodal metastasis for these tumours would be less than 5% and that the predicted 10-year survival rate would be about 90%.

More recently, the upper limit of tumour size for the invasive process has been expanded to include tumours as large as 1 cm in diameter,[2] but of far greater importance is whether the term minimal breast cancer is one that defines a true entity. From a biologic standpoint, the grouping together of intraductal carcinoma, lobular carcinoma in situ and invasive cancer (regardless of diameter) appears inappropriate. Clearly, these three processes represent distinct diseases, having unique biologic characteristics. A possible justification for maintaining a definition that includes disparate components might be to signify uniformity in therapeutic management, but since the therapeutic aspects of minimal breast cancer are more complex than the definition, it is unlikely that the term will survive on the strength of this aspect. In fairness to Gallager and Martin, the definition of minimal breast cancer was formulated at a time when insufficient attention was being paid to categories of breast cancer with favourable prognostic characteristics. Any criticism should be directed towards current investigators who have maintained the term in spite of a better understanding of the biology of the diseases. Accordingly, I shall emphasize the individuality of the three components of minimal breast cancer rather than attempt a collective analysis based on an outmoded concept.

Even if one were to accept the term

minimal breast cancer, it has been argued that the number of patients meeting the specified criteria would be very small indeed. Data from well-established tumour registries[3,4] estimate that only 10% of all breast cancers diagnosed could be considered as minimal breast cancer (Table I). There is good reason to believe, however, that the overall detection of the three components of minimal breast cancer is changing as a direct result of the increasing popularity and implementation of screening programs. Data from the Breast Cancer Detection Demonstration Projects (BCDDP) disclosed that minimal breast cancer accounted for more than 40% of cancers detected at the first screening.[2] Of these, noninfiltrating cancer constituted more than 25% of all detected breast cancers. Of the noninfiltrating cancers, 80% were intraductal and 20% were lobular carcinomas in situ.

In-depth analysis of the individual components of minimal breast cancer is thus not only compelling, but necessary. With the development of screening modalities that can identify more patients with minimal breast cancer, well-controlled prospective studies designed to assess the biologic behaviour of noninfiltrating breast cancer are essential.

Lobular Carcinoma in Situ

The therapeutic preferences for this type of cancer have largely been determined by how the disease was perceived biologically. Two mutually exclusive hypotheses have been formulated to describe the disease. Proponents of the first and most popular hypothesis regard lobular carcinoma in situ as the direct progenitor of invasive cancer, given enough time. Consequently, they have treated this cancer by performing at least an ipsilateral mastectomy. In the second hypothesis, lobular carcinoma in situ is regarded simply as a marker of a population at high risk for the development of subsequent invasive cancer which is not related to the initial lobular carcinoma in situ. The therapy that the surgeon selects invariably reflects his biologic understanding of the disease.

Before therapeutically relevant issues are considered, it is important to review the behaviour and natural history of the disease. Since lobular carcinoma in situ was defined as a distinct entity in 1941 by Foote and Stewart[3] and independently by Muir,[4] it has been known that the entity is inconspicuous, both on clinical and gross examinations. It occurs at an earlier age than ductal cancer, with 75% of all cases being documented between the ages of 40 and 54 years.[5,6] The entity was observed predominantly, but not exclusively, in premenopausal women.[7,8] A property that has often been cited as a justification for performing mastectomy is the propensity towards multicentricity. Although noninfiltrating multicentric tumours were evident in 10% to 60% of all women with lobular carcinoma in situ, the incidence of multicentric infiltrating cancer was less than 5%.[9-11] In addition, bilateral disease has been demonstrated in approximately 35% of cases.[12,13]

Because surgeons have generally regarded lobular carcinoma in situ as the progenitor of invasive cancer, mastectomy has been the most popular therapy. This has eliminated the opportunity to study the consequences of the disease following biopsy only and thus an opportunity to understand the natural history of the disease has been lost. All the data derived for lobular carcinoma in situ not treated by mastectomy were obtained from retrospective and anecdotal case reports.

A review of four of the principal series dealing with patients who had lobular carcinoma in situ treated only by biopsy[7,14-16] disclosed that the number of documented cases was inadequate, ranging from 32 to 263; moreover, the mean follow-up varied from 15 to 24 years (Table II).

Clearly, the most critical property of lobular carcinoma in situ that will influence the choice of therapy is the incidence of invasive cancer subsequently. Here, too, there is a wide variation ranging from a 13% incidence of invasive cancer in the series of Wheeler and colleagues[14] to a high of 31% in the series reported by Rosen and associates.[7] It is interesting that the interval from diagnosis of the lobular carcinoma to that of invasive cancer ranged from 15 to 20 years. Perhaps, the most fascinating aspect of the subsequent infiltrating cancer is that it is not restricted to the ipsilateral breast, but occurs with equal frequency in the contralateral breast.[7,16] Curiously, the histologic features of the subsequent invasive cancer in the majority of instances is not lobular as one might expect if lobular carcinoma in situ had progressed to the invasive form, but is ductal in approximately 60% of cases. Despite some interesting theories suggesting that lobular and ductal cancer have similar anatomic origins,[17] the preponderance of infiltrating ductal cancer following lobular carcinoma in situ supports the hypothesis that lobular cancer is a high-risk marker, not a precursor.

In summary, lobular carcinoma in situ is a fascinating multicentric and bilateral entity. Twenty-five percent of patients with this type of cancer will have invasive cancer subsequently and the majority of the invasive cancers will be of ductal type. On average, more than 15 years will pass before the development of invasive cancer and the contralateral breast is at equal risk for such development. Because invasive cancer may develop bilaterally, whatever treatment is advocated for the ipsilateral breast should also be advocated for the contralateral breast. Based on the data, in the opinion of our group the risk of invasive cancer does not justify bilateral prophylactic mastectomy; consequently, a predefined follow-up regimen is the preferred method of dealing with this disease. At present, we perform an adequate local excision of the lobular carcinoma with no further operative treatment. Because of the very low incidence (about 1%) of regional node metastases from this disease, we do not think that axillary node dissection is warranted.

With respect to treatment of the contralateral breast, a random or mirror-image biopsy is meddlesome in our opin-

Table I—Minimal Breast Cancer as Percentage of All Diagnosed Cases

	Study		
Type of cancer	SEER, 1978[25]	ACS, 1980[5]	BCDDP, 1979[2]
Minimal	9	12	41
Noninfiltrating	5	3	26
Infiltrating < 1 cm	4	9	15

SEER = Surveillance Epidemiology and End Results Reporting, ACS = American College of Surgeons, BCDDP = Breast Cancer Detection Demonstration Projects.

Table II—Risk of Invasive Cancer Following Lobular Carcinoma in Situ

	Series, yr			
	Wheeler and colleagues, 1974[14] (n = 32)	Andersen, 1977[15] (n = 44)	Rosen and colleagues, 1979[7] (n = 99)	Haagensen and colleagues, 1981[16] (n = 263)
Mean follow-up, yr	18	15	24	15
Subsequent invasive cancer risk				
Ipsilateral, %	4	20	18	11
Contralateral, %	9	9	14	9
Overall risk, %	13	25	31	17

ion and has little place in our therapeutic approach. The current reappraisal of the therapy for invasive cancer will undoubtedly be a major influence on the treatment of lobular carcinoma in situ. Preliminary results indicate that for some patients there is no disadvantage to breast-preserving operations. If these findings are substantiated, then the proponents of mastectomy for lobular carcinoma in situ will find themselves in the difficult position of advocating prophylactic therapy more severe than the treatment of the disease they are trying to prevent. Until a therapeutic regimen can be evolved, based on reliable prospective data, we recommend that patients with lobular carcinoma in situ not be subjected to mastectomy but to local excision with follow-up consisting of physical examinations every 3 to 6 months and mammography annually.

Intraductal Cancer

If the data on lobular carcinoma in situ can be described as scanty, that on intraductal cancer may be characterized as seriously deficient. In the former case, because the disease was not recognized by all as a neoplastic entity until relatively recently, and because several investigators chose to regard the disease as a noncarcinoma, cases were available in which the patient had not undergone mastectomy. The same considerations are not applicable to intraductal carcinoma. Patients with a diagnosis of intraductal carcinoma were invariably treated by mastectomy, and the major point of contention was not whether a mastectomy should be performed, but whether a concomitant axillary node dissection was necessary. As a result, few patients could be identified who had not had mastectomy; once again, an opportunity to evaluate the behaviour of the disease was lost. In spite of the paucity of definitive studies exploring the natural history of intraductal carcinoma, there are sufficient examples in the literature to indicate that noninvasive intraductal cancer of the breast possesses biologic characteristics distinct from those of lobular carcinoma in situ.

Of those patients with noninfiltrating breast cancer, the ratio of intraductal carcinoma to lobular carcinoma is approximately 2 to 1. The diseases differ with respect to age distribution: the greatest number of patients with lobular carcinoma is found in the 45- to 54-year age group with a rapid decrease in subsequent years, while the number of patients with intraductal cancer is fairly constant for women 55 years of age and older.[5] Whether this is a result of different etiologic mechanisms for the two diseases or because lobular carcinoma is hormone dependent and intraductal cancer is not remains speculative. Irrespective of etiologic considerations, the differences underscore the distinct behavioural characteristics of the two conditions.

As with lobular cancer, the most important therapeutic property is the incidence of invasive cancer following a diagnostic biopsy. Examples of the available data on this aspect of intraductal cancer are shown in Table III.[18-20] All three studies were retrospective and suffered from small sample sizes. Of patients in whom a diagnosis of intraductal carcinoma is made, 25% to 50% will allegedly have infiltrating cancer, on average 10 years from the time of initial biopsy. Although this disease has a greater than 50% frequency of ipsilateral multicentricity, almost all the invasive cancers occur not only in the same breast, but in the same quadrant as the initial tumour.[19,20] The histologic type of invasive cancer is exclusively ductal.

In addition to the property of multicentricity, from 5% to 20% of patients with intraductal cancer reportedly have residual foci of invasive cancer on examination of multiple histologic sections of the ipsilateral breast; however, when the criteria for intraductal carcinoma were rigidly defined, this figure was closer to 5%.[9] Finally, there have been documented instances[21,22] in which 1% to 5% of patients with intraductal carcinoma and no evidence of infiltration on microscopy had ipsilateral axillary lymph-node metastases. A summary and contrast of the properties of lobular carcinoma in situ and intraductal carcinoma appears in Table IV. The retrospective nature and methodologic weakness of the studies available on intraductal carcinoma emphasize the error of drawing firm conclusions on the behaviour of this disease. Nevertheless, some of these characteristics have been interpreted as suggesting that intraductal carcinoma is merely a precursor of invasive cancer and that, given sufficient time, invasive cancer will develop from a residual focus in a defined percentage of patients.

On the basis of this biologic interpretation of the properties attributed to intraductal cancer, an ipsilateral mastectomy with a low axillary dissection has become the most popular therapy for this disease. The lack of data documenting its natural history does not justify a complacent attitude in accepting this therapeutic approach. The pivotal question in the operative management concerns the role of breast-preserving operations with or without axillary node dissection. Several retrospective analyses address the value of breast-preserving operations in this disease. The American College of Surgeons National Breast Cancer Survey Study[5] reported on 202 patients with intraductal carcinoma treated according to the dictates and preferences of the individual surgeon. Treatment failures were identical in patients treated with mastectomy (with and without axillary dissection) and those treated with breast-preserving operations, with 65% of the patients alive and free of disease at 5 years in both groups. In spite of these findings, indicating no difference, the American College of Surgeons group seems disinclined to accept its own analysis and concluded that total mastectomy with low axillary dissection or modified radical mastectomy represents the optimal therapy for intraductal carcinoma.

Preliminary results of the MD Anderson Hospital experience with intraductal carcinoma warrant further comment. In

Table III—Risk of Invasive Cancer Following Intraductal Carcinoma

	Series, yr		
	Farrow, 1970[18] (n = 25)	Betsill and colleagues, 1978[19] (n = 15)	Page and colleagues, 1982[20] (n = 25)
Mean follow-up, yr	–	22	15
Subsequent invasive cancer, %	20	53	28
Interval to subsequent cancer, yr	1–8	10	6

Table IV—Properties of Noninvasive Breast Cancer

Property	Lobular carcinoma in situ	Intraductal carcinoma
Initial lesion		
Multicentricity, %	60	60
Residual invasive cancer, %	5	5–20
Subsequent invasive cancer		
Occurrence, %	25	25–55
Laterality	Bilateral	Ipsilateral
Approximate interval to occurrence, yr	20	10
Histologic type	Ductal	Ductal

70 consecutive patients treated with local excision and radiotherapy to the ipsilateral breast, there has been only one recurrence in the untreated ipsilateral axilla after a minimum of 3 years follow-up (Montague E: Personal communication, 1985).

The most compelling justification for performing mastectomy in women with intraductal carcinoma comes from two recently completed studies,[23,24] assessing quandrantectomy and segmental mastectomy in patients with invasive cancer. As with lobular carcinoma in situ, the increasing acceptance of breast-preserving operations for invasive disease will make prophylactic mastectomy considerably more difficult to justify. To resolve the therapeutic dilemma with respect to intraductal carcinoma, a carefully controlled, prospective, randomized, clinical trial, designed to determine the natural history as well as the appropriate treatment intervention, must be carried out. Such a trial has currently been proposed for implementation at a national level by the National Surgical Adjuvant Breast Project (NSABP) (Fig. 1). The inclusion of a group of patients treated by local excision (with free margins) will identify the role of putative prognostic discriminants in the occurrence of subsequent invasive disease (such as tumour size and multifocality). The second arm will address the propriety of adjuvant radiotherapy to the remaining breast and determine whether this regimen represents acceptable therapy.

Invasive Adenocarcinoma

Clinically and biologically, patients with infiltrating tumours demonstrate no unique features that would justify the arbitrary designation of tumour diameter less than 1 cm. It is not tumour size but the histologic status of the axillary nodes that is the most important predictor of prognosis. Now that sampling of axillary nodes is almost routine, regardless of the primary breast operation, the use of tumour size alone as a prognostic variable is anachronistic, as may be illustrated by correlating tumour size with the presence or absence of histologically positive ipsilateral axillary nodes. Examination of data from more than 8000 patients in the SEER survey[25] disclosed that more than 17% of patients with tumours less than 0.5 cm in diameter had axillary nodes that were histologically positive for cancer; this figure rose to more than 20% in tumours less than 1 cm in diameter. Although tumour size provides some indication of the histologic status of the axilla, it should not be used alone to predict prognosis. The identification of patients according to tumour size (small or otherwise) without information on the status of axillary nodes should be avoided. The designation of patients with tumours less than 1 cm in diameter as a distinct subset and their inclusion in minimal breast cancer is inappropriate biologically. Therapeutically, it is equally misguided to include small invasive neoplasms in the same category as noninfiltrating cancer. The value of breast-preserving operations for small invasive cancers as well as invasive cancers 4 cm in diameter or smaller will be defined by the recently completed NSABP, protocol B-06.[24] In this study, a substantial proportion of the patients entered had invasive cancer 1 cm in diameter or smaller. Over 2100 patients were randomized to three treatment arms: (a) modified radical mastectomy, (b) segmental mastectomy and axillary node dissection or (c) segmental mastectomy, axillary node dissection and radiotherapy to the remaining ipsilateral breast. The preliminary results from this study confirm that to categorize tumours less than 1 cm in diameter as a separate subset is specious.

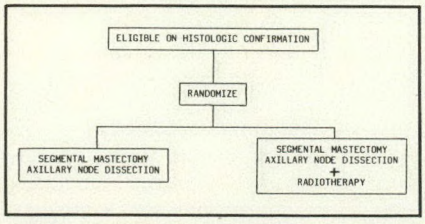


FIG. 1—Proposed NSABP controlled, prospective, randomized, clinical trial for intraductal breast cancer.

References

1. GALLAGER HS, MARTIN JE: An orientation to the concept of minimal breast cancer. *Cancer* 1971; 28: 1505-7
2. Report of the working group to review the National Cancer Institute-American Cancer Society Breast Cancer Detection Demonstration Projects. *JNCI* 1979; 62: 639-709
3. FOOTE FW JR, STEWART FW: Lobular carcinoma *in situ;* rare form of mammary cancer. *Am J Pathol* 1941; 17: 491-6
4. MUIR R: Evolution of carcinoma of mamma. *J Pathol Bacteriol* 1941; 52: 155-72
5. ROSNER D, BEDWANI RN, VANA J, BAKER HW, MURPHY GP: Noninvasive breast carcinoma: results of a national survey by the American College of Surgeons. *Ann Surg* 1980; 192: 139-47
6. HAAGENSEN CD, LANE N, LATTES R, BODIAN C: Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer* 1978; 42: 737-69
7. ROSEN PP, KOSLOFF C, LIEBERMAN PH, ADAIR F, BRAUN DW JR: Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. *Am J Surg Pathol* 1978; 2: 225-51
8. ROSEN PP, SENIE RT, FARR GH, SCHOTTENFELD D, ASHIKARI R: Epidemiology of breast carcinoma: age, menstrual status, and exogenous hormone usage in patients with lobular carcinoma in situ. *Surgery* 1979; 85: 219-24
9. ROSEN PP, SENIE R, SCHOTTENFELD D, ASHIKARI R: Noninvasive breast carcinoma: frequency of unsuspected invasion and implications for treatment. *Ann Surg* 1979; 189: 377-82
10. SHAH JP, ROSEN PP, ROBBINS GF: Pitfalls of local excision in the treatment of carcinoma of the breast. *Surg Gynecol Obstet* 1973; 136: 721-5
11. CARTER D, SMITH RR: Carcinoma in situ of the breast. *Cancer* 1977; 40: 1189-93
12. URBAN JA: Bilaterality of cancer of the breast. Biopsy of the opposite breast. *Cancer* 1967; 20: 1867-70
13. SNYDER RE: Mammography and lobular carcinoma in situ. *Surg Gynecol Obstet* 1966; 122: 255-60
14. WHEELER JE, ENTERLINE HT, ROSEMAN JM, TOMASULO JP, MCILVAINE CH, FITTS WT JR, KIRSHENBAUM J: Lobular carcinoma in situ of the breast. Long-term followup. *Cancer* 1974; 34: 554-63
15. ANDERSEN JA: Lobular carcinoma *in situ* of the breast. An approach to rational treatment. *Cancer* 1977; 39: 2597-602
16. HAAGENSEN CD, BODIAN C, HAAGENSEN DE JR: *Breast Carcinoma — Risk and Detection,* Saunders, Philadelphia, 1981
17. JENSEN HM, WELLINGS SR: Preneoplastic lesions of the human mammary gland transplanted into the nude athymic mouse. *Cancer Res* 1976; 36(7 pt 2): 2605-10
18. FARROW JH: Current concepts in the detection and treatment of the earliest of the early breast cancers. *Cancer* 1970; 25: 468-77
19. BETSILL WL JR, ROSEN PP, LIEBERMAN PH, ROBBINS GF: Intraductal carcinoma. Long-term follow-up after treatment by biopsy alone. *JAMA* 1978; 239: 1863-7
20. PAGE DL, DUPONT WD, ROGERS LW, LANDENBERGER M: Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer* 1982; 49: 751-8
21. OZZELLO L: Ultrastructure of the human mammary gland. *Pathol Annu* 1971; 6: 1-59
22. Idem: Ultrastructure of intra-epithelial carcinomas of the breast. *Cancer* 1971; 28: 1508-15
23. VERONESI U, SACCOZZI R, DEL VECCHIO M, et al: Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981; 305: 6-11
24. FISHERB, et al: Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985; 312: 665-73
25. SMART CR, MYERS MH, GLOECKLER LA: Implications from SEER data on breast cancer management. *Cancer* 1978; 41: 787-9

NOTICES

Cleft Palate and Related Craniofacial Anomalies

The 5th International Congress on Cleft Palate and Related Craniofacial Anomalies will be held Sept. 2–7, 1985 at the Congress Center in Monte Carlo.

This congress will be of interest to all practitioners concerned with this subject, including plastic, dental, pediatric and maxillofacial surgeons, orthodontists and otorhinolaryngologists.

For further information contact Dr. René Malek, Chairman, International Congress on Cleft Palate and Related Craniofacial Anomalies, 6, rue Erlanger, 75016 Paris, France; or write SOCFI, 14, rue Mandar, 75002 Paris, France.

Reflux Esophagitis and the Angelchik Prosthesis

A medical and surgical review of reflux esophagitis and the Angelchik prosthesis, presented by the departments of surgery and continuing medical education at the University of Wisconsin, is being held June 14-15, 1985 at the Concourse Hotel in Madison, Wisconsin. The conference is accredited for 11 hours in AMA Category 1.

For further information contact: Sarah Z. Aslakson, Department of Continuing Medical Education, 465B Warf Building, 610 Walnut St., Madison, WI 53705, USA; (608) 263-2856.

Thoracic and Cardiovascular Surgery

The 7th Asian Congress of Thoracic and

continued on page 267

WALLEY J. TEMPLE, MD, FRCSC*

4. Surgical Management of the Patient at High Risk for Breast Cancer

The most controversial aspect of breast disease centres around the management of patients who have either a strong family history of breast cancer or a biopsy diagnosis of lobular carcinoma in situ or ductal carcinoma in situ. The current alternatives for patients who have two or more relatives with breast cancer consist of close follow-up or prophylactic total mastectomies and reconstruction.

Invasive breast cancer in patients with lobular carcinoma in situ may occur in either breast and may be as high as 30% at 20 to 30 years. In these women it is reasonable to do a wide excision of the lobular carcinoma; in those without a family history, close follow-up is adequate. Intraductal cancer treated by biopsy only is associated with a 40% risk of cancer in the ipsilateral breast. Therefore, the usual management is total mastectomy. However, the information to support this therapy over a segmental resection has limited scientific validity.

Because the cosmetic appearance after total mastectomy and reconstruction is not as good as that of the normal breast, this procedure must be employed cautiously and only with the total support of the patient and her husband or close family. Subcutaneous mastectomy for prophylaxis leaves behind macroscopic glandular tissue and, therefore, is not considered by many to be optimal management. A total mastectomy, preserving the skin and resecting all macroscopic breast tissue and nipple, is the treatment of choice if the procedure is deemed appropriate.

L'aspect le plus discuté des maladies du sein tourne autour du traitement de la patiente qui possède de solides antécédents familiaux de cancer du sein ou de celle chez qui on a diagnostiqué, à la biopsie, un carcinome lobulaire in situ ou un cancer canaliculaire in situ. Les choix qui s'offrent actuellement aux patientes qui comptent plus d'une victime du cancer du sein dans leur famille sont la surveillance étroite ou la mastectomie prophylactique totale avec conservation de la peau et reconstruction.

Chez la patiente atteinte d'un carcinome lobulaire in situ, un cancer invasif peut apparaître dans un ou l'autre sein et sa fréquence peut atteindre 30% après 20 à 30 ans. Il est raisonnable chez ces femmes de procéder à une excision large du carcinome lobulaire; chez celles qui n'ont pas d'antécédents familiaux, une surveillance étroite est suffisante. Les cancers canaliculaires traités par biopsie seulement sont reliés à un risque de 40% de cancer dans le sein ipsilatéral. En conséquence, le traitement habituel consiste à réaliser une mastectomie totale. Toutefois la préférence pour cette intervention par rapport à la résection segmentaire repose sur une preuve scientifique limitée.

Comme l'apparence cosmétique après mastectomie totale et reconstruction n'est pas aussi bonne que celle d'un sein normal, on doit recourir à cette opération avec précaution et seulement après avoir obtenu l'appui complet de la patiente et de son conjoint ou de sa famille immédiate. La mastectomie sous-cutanée à visées prophylactiques laisse du tissu glandulaire macroscopique et ne peut donc être considérée comme un traitement optimum. Une mastectomie totale avec conservation de la peau et résection de tout le tissu mammaire macroscopique ainsi que du mamelon, représente le traitement de choix quand cette intervention semble appropriée.

From the Tom Baker Cancer Centre, Calgary, Alta.

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

**Director of Surgery, Tom Baker Cancer Centre; Chief, Division of Surgical Oncology, Department of Surgery, Foothills Hospital, University of Calgary*

Accepted for publication Feb. 4, 1985

Reprint requests to: Dr. Walley J. Temple, Director of Surgery, Tom Baker Cancer Centre, 1331 - 29th Street NW, Calgary, Alta. T2N 4N2

The dilemma of how to treat the patient at high risk for invasive breast cancer has become increasingly apparent. As a result of breast screening programs, the accessibility of mammography and, in general, a heightened awareness of health issues, the illness is now detected early in its course. In fact, many women, especially those with a family history of breast cancer, now consult the physician about the particular risk for breast cancer disease and request alternative management. Treatment at this stage continues to be an insoluble problem because our predictive ability for any one patient is far from perfect and the solutions are still unsatisfactory. Nevertheless, a review of data currently available helps to formulate a plan for each situation.

Family History

Traditionally, we have considered the patient with a previous history of breast cancer as being at the highest risk for a subsequent metachronous lesion. This risk averages 1% per year or 15% in the woman's lifetime. It has not been our practice to recommend prophylactic mastectomy in these circumstances, although its use has certainly been considered by surgeons in the past. However, it is now recognized that a particularly high-risk group for the development of a subsequent metachronous lesion are those patients who also have a family history of breast cancer.[1] In a study of 198 such patients, the incidence of a second cancer was three times that for patients with no family history of breast cancer. The projected cumulative risk at 20 years in premenopausal patients was 46% while the actual occurrence was 37%.[1] In postmenopausal patients who had a much shorter follow-up, the occurrence of breast cancer was only 5.8% after 4 years. Therefore, if one considers a prophylactic contralateral mastectomy and reconstruction as a reasonable form of management in this subset of patients, candidates would certainly include premenopausal women with stage I breast cancer or those who have been followed up for at least 5 years.

Patients with a family history of breast cancer are also at risk for an initial primary breast cancer.[2,3] This group comprises women with two or more first-degree relatives, including paternal relatives, who have been affected by the disease. It is not generally realized that although men rarely have breast cancer, they readily transmit this tendency to their progeny. A family history results not only in a higher incidence of bilateral disease, as already discussed, but also a much younger age at presentation. This transmission of risk is most potent (47-fold in one report) if the family members were premenopausal at the time of diagnosis and both breasts were ultimately affected. If the family members were postmenopausal with bilateral foci of cancer, the risk was greater by a factor of four and translated into an 11% incidence of breast cancer in the relatives.[3] If only one breast was involved in the affected family member, the risk for the family was not much greater than in the normal population. The study did not define the risk in women who present with three or more first-degree relatives with breast cancer. The risk in these women is much greater than 30%, probably approaching 100% in some. In such situations, the risk must be estimated more by clinical judgement than by available data. It is in these patients that one can make the strongest case for prophylactic mastectomy and reconstruction.

Fibrocystic Disease

The most frequent clinical problem that we deal with is fibrocystic disease which is reputed by some to be at high risk for progression to invasive cancer. Although fibrocystic disease has often been implicated as a predisposing factor, the available data suggest that the increased risk is probably conferred only on those with a proliferative lesion who have required a breast biopsy. There is much less information on the exact risk of other benign lesions, such as papillomatosis or atypical ductal hyperplasia. However, in the study of Haagensen and colleagues[4] who had 51 patients with a follow-up ranging from 13 to 32 years, multiple sites of ductal papillomatosis in the breast resulted in a higher incidence of breast cancer of approximately 10%. In general, when a biopsy shows a benign condition, a prophylactic surgical procedure is not justified unless there are other extenuating circumstances.

Carcinomas in Situ

The most extensively documented group of high-risk women are those with carcinoma in situ. These women have traditionally been categorized as having minimal breast cancer and have included patients with infiltrative cancers less than 0.5 cm to 1.0 cm in diameter. These tumours should no longer be considered minimal, because the incidence of lymph-node metastases ranges from 10% to 20%.[5] The two in-situ lesions, ductal and lobular, have a different natural history. Ductal carcinoma in situ is the more aggressive lesion. In five series of approximately 80 patients, a subsequent carcinoma developed exclusively in the ipsilateral breast in 39%. This occurred in the first 10 years of follow-up.[5,6] A more careful histologic examination of these lesions has revealed a microinfiltrative component in 20%. This also explains why 5% of these patients will have metastatic axillary lymph nodes. The opposite breast is not at inordinate risk for a second primary tumour.[6]

Lobular carcinoma in situ is a less-frequent diagnosis; 90% of these patients are younger than 55 years. A subsequent cancer is found in only 20% of these patients after 15 years of follow-up, with each breast being equally at risk.[4] This is not surprising as a mirror-image biopsy is positive in about one third of these patients. Axillary involvement is found in less than 1% of these women. A rational management in these patients is particularly controversial with treatments varying from the simple biopsy, to modified radical mastectomy, to bilateral subcutaneous mastectomies. There is no consensus as to the best treatment but it is fair to comment that there are two rational choices. One is to treat the diagnosis as an indication of future high risk and provide close clinical follow-up. The second option is to eliminate all subsequent potential for breast cancer by performing bilateral total mastectomy.

Indications for Prophylactic Procedures

With these facts in hand, it is important to emphasize that prophylactic mastectomies are only reasonable in very selected circumstances. First, a gradation of perceived risk exists for most of these patients and its determination is more often an educated guess than easily established scientific fact. Some patients, such as those with a diagnosis of lobular carcinoma in situ, will be terrified by the prediction of a 20% risk of cancer, while others with a family history suggesting a 50% risk or more will be comfortable with close follow-up. Any discussion of prophylactic surgery must be held with this in mind. The procedure should not be considered seriously unless the husband and family give their full support and enough time has been taken to ensure a rational decision. Until plastic surgical reconstruction reliably mimics a real breast, one has to be convinced of the overall health benefits before doing a procedure that may result in a cosmetically unattractive appearance. At the same time, one must realize that even in patients with stage I disease, long-term cure is only 54%, although at 10 years 70% to 80% are disease free.[7] This is a very reasonable risk at 60 to 70 years of age but not so palatable at 40 to 50 years.

If prophylactic surgery is determined to be the best course for a particular patient, then it is important to do the right operation. In women with multiple papillomatosis or intraductal carcinoma, a unilateral mastectomy is indicated. In the latter group, an axillary dissection is also reasonable.[6] In patients with a high-risk family history or with lobular carcinoma in situ, a bilateral mastectomy is necessary for prophylaxis. One must recognize that many surgical procedures have been used to treat in-situ carcinoma, ranging from biopsy to radical mastectomy for the ductal type or to bilateral total mastectomy for the lobular type. Although the findings of a survey conducted by the American College of Surgeons on minimal breast cancer do not show an advantage for any approach, the short follow-up of 5 years renders this observation meaningless.[8]

Subcutaneous Mastectomy

The use of subcutaneous mastectomy for these women with our present state of knowledge is not optimal.[9-13] This operation leaves breast tissue behind skin flaps, scars, nipples and probably in the axilla. Many plastic surgeons have had experience of carcinoma developing in one or two patients who had previously undergone subcutaneous mastectomy.[10,11] In the animal model, partial excision of breast tissue does not lower the propensity for subsequent breast cancer.[14] Therefore, a meticulous total mastectomy is essential to eliminate future worry of a subsequent cancer. Even this is tempered by the knowledge that, occasionally, microscopic rests in the muscle or adjacent to the dermis may remain.[9] It has been suggested that injection of the lactiferous ductal system with methylene blue would provide a visual assurance of complete removal of all breast tissue. This should be examined further.[9] A prophylactic total mastectomy is, in fact, similar to a cancer operation except that the entire skin covering can be preserved. The best incision is a radial one encircling the nipple and extending laterally, as it is easily hidden by the brassière. It provides equal surgical access to all parts of the breast, especially to the axillary tail. This incision does not diminish a subsequent satisfactory cosmetic result. The reconstruction problems resulting from thin skin flaps are largely overcome by submuscular placement of the prosthesis.


EMERGENCY

Conclusions

The concept of prophylactic breast surgery is not new. It is used in certain patients to prevent colonic cancer, cervical cancer and thyroid cancer. Because of the psychosexual importance of the breast in our society and the fact that reconstruction has not been perfected, the ideal treatment for high-risk patients has not evolved. The indications for such a procedure depend not only on the relative risk of breast cancer developing but, more importantly, on the patient's feelings about this risk and her and her husband's ability to cope with a potentially poor cosmetic result. Prophylactic mastectomy is indicated, but only in very carefully selected patients. If there is any doubt, one's bias should be towards careful, close follow-up.

References

1. HARRIS RE, LYNCH HT, GUIRGIS HA: Familial breast cancer: risk to the contralateral breast. *J Natl Cancer Inst* 1978; 60: 955-60
2. ANDERSON DE: Genetic study of breast cancer: identification of a high risk group. *Cancer* 1974; 34: 1090-7
3. Idem: A genetic study of human breast cancer. *J Natl Cancer Inst* 1972; 48: 1029-34
4. HAAGENSEN CD, BODIAN C, HAAGENSEN DE JR: *Breast Carcinoma — Risk and Detection*, Saunders, Philadelphia, 1981: 197-291
5. WOLMARK N: Minimal breast cancer — a major therapeutic dilemma. In MARGOLESE RG (ed): *Contemporary Issues in Clinical Oncology. Breast Cancer*, Livingstone, New York, 1983: 123-50
6. PAGE DL, DUPONT WD, ROGERS LW, LANDENBERGER M: Intraductal carcinoma of the breast: follow-up after biopsy only. *Cancer* 1982; 49: 751-8
7. RUTQVIST LE, WALLGREN A, NILSSON B: Is breast cancer a curable disease? A study of 14,731 women with breast cancer from the Cancer Registry of Norway. *Cancer* 1984; 53: 1793-800
8. ROSNER D, BEDWANI RN, VANA J, BAKER HW, MURPHY GP: Noninvasive breast carcinoma: results of a national survey by the American College of Surgeons. *Ann Surg* 1980; 192: 139-47
9. HICKEN NF: Mastectomy; a clinical pathologic study demonstrating why most mastectomies result in incomplete removal of the mammary gland. *Arch Surg* 1940; 40: 6-14
10. HUMPHREY LJ: Subcutaneous mastectomy is not a prophylaxis against carcinoma of the breast: opinion or knowledge?(E) *Am J Surg* 1983; 145: 311-2
11. MCCARTY KS JR, KESTERSON GH, WILKINSON WE, GEORGIADE N: Histopathologic study of subcutaneous mastectomy specimens from patients with carcinoma of the contralateral breast. *Surg Gynecol Obstet* 1978; 147: 682-8
12. PENNISI VR, CAPOZZI A: The incidence of obscure carcinoma in subcutaneous mastectomy. Results of a national survey. *Plast Reconstr Surg* 1975; 56: 9-12
13. SNYDERMAN RK: Prophylactic mastectomy: pros and cons. *Cancer* 1984; 53(3 suppl): 803-8
14. JACKSON CF, PALMQUIST M, SWANSON J, WONG J, MILLER SH, DEMUTH RJ, FLETCHER WS: The effectiveness of prophylactic subcutaneous mastectomy in Sprague-Dawley rats induced with 7,12-dimethylbenzanthracene. *Plast Reconstr Surg* 1984; 73: 249-60

BOOK REVIEWS

CARDIAC PATHOLOGY. An Integrated Text and Colour Atlas. Anton E. Becker and Robert H. Anderson. 248 pp. Illust. Raven Press, New York, 1983. $80 (US). ISBN 0-89004-972-6.

The 16 chapters of this book are equally divided between acquired and congenital cardiac lesions. One, on cardiac adaptation, deals with hypertrophy and dilatation and another with interactions between the heart and lungs. In six chapters, a variety of acquired heart diseases and the pathologic features of the aging heart are considered. The separation of "cardiac lacerations" into a chapter seemed artificial to me. The lesions illustrated could have been included in other sections.

Of the chapters devoted to congenital heart diseases, the anatomy of heart chambers and of vessels leaving the heart, allowing their recognition, is defined in one chapter, which also contains a discussion of chamber relationships to permit definition of anomalies and to provide a basis for diagnosing congenital heart disease. The lesions so defined are dealt with in subsequent chapters. A non-expert, on first reading, might have difficulty in understanding the text, but persistence is rewarding.

The illustrations are, for the most part, superb. The quality of reproduction of Fig. 1.11 and some of the low-power photomicrographs was poor in my copy. Most photographs are in colour. Many are complemented by explanatory line drawings. They and the diagrams, which are simple and pleasingly presented, are most useful. The text is succinct, emphasizing the functional, and has pertinent, if sometimes wonderfully selective, references.

I enjoyed the book and would recommend it to cardiovascular pathologists, cardiologists, cardiovascular surgeons, pediatricians and all interested in heart diseases. All pathology and cardiology department libraries should have a copy. Even if a reader is not satisfied with the text, because the book is not intended to be encyclopedic, it is worth having because it is a splendid atlas of heart lesions or, as the authors prefer, "a work of art".

MALCOLM D. SILVER, MD, PH D, FRCPC

Professor and Chairman,
Department of Pathology,
University of Western Ontario,
London, Ont.
N6A 5C1

COLOR ATLAS OF CARDIAC SURGERY. Acquired Heart Disease. James L. Monro and Gerald Shore. 165 pp. Illust. Appleton-Century-Crofts, East Norwalk, Conn., 1982. $110. ISBN 0-8385-1164-3.

This atlas follows commonly performed operations for acquired heart disease step by step. It covers the gamut of operations, beginning with median sternotomy and cardiopulmonary bypass and continuing through the various valve operations, coronary artery surgery, complications of coronary disease such as left ventricular aneurysm and acquired ventricular septal defect, and surgery of the intrathoracic aorta. General principles of cardiac surgery are well presented but the book reflects the bias of the authors by specifically pointing out their

continued on page 271

STEPHAN ARIYAN, MD, FACS

5. Prophylactic Mastectomy for Precancerous and High-Risk Lesions of the Breast

The candidates for prophylactic mastectomy are those who have a family history of breast cancer, multiple fibrocystic masses that have been biopsied or are too numerous to biopsy appropriately, or patients who previously have had cancer in one breast. The decision to perform the subcutaneous mastectomy is one that must be made by the surgeons involved, in consultation with the patient and her husband. The data from subcutaneous mastectomies appear promising and the technical results have improved as experience has been gained. However, 5 to 10 more years are necessary to determine whether this procedure decreases the incidence of breast cancer in these high-risk patients.

Les candidates à une mastectomie prophylactique sont les patientes qui ont des antécédents familiaux de cancer du sein, celles qui ont des masses fibrokystiques multiples qui ont été biopsiées ou qui sont trop nombreuses pour l'être, ou les patientes qui ont déjà eu un cancer du sein. La décision de procéder à une mastectomie sous-cutanée doit être prise par le chirurgien en consultation avec la patiente et son conjoint. Les résultats de la mastectomie sous-cutanée semblent prometteurs et les résultats techniques se sont améliorés avec l'expérience. Toutefois, il faudra de 5 à 10 ans pour déterminer si cette opération réduit la fréquence du cancer du sein chez les patientes à risque.

From the Department of Plastic and Reconstructive Surgery, Yale University School of Medicine, New Haven, Conn.

Presented as part of a symposium on precancerous and high-risk lesions of the breast by the Royal College of Physicians and Surgeons of Canada, in cooperation with the Canadian Association of General Surgeons, the Canadian Oncology Society and the Canadian Society of Plastic Surgeons, Montreal, PQ, Sept. 11, 1984

Accepted for publication Jan. 7, 1985

Reprint requests to: Dr. S. Ariyan, Professor of Surgery, Chief, Plastic and Reconstructive Surgery, Yale University School of Medicine, 116 FMB, PO Box 3333, New Haven, CT 06510, USA

In the mind of the public, breast reconstruction is often a matter of surgery saddled with myths. (Many patients have a great interest in the subject, and to advise them properly on the action to take, we need to re-evaluate the entire area.) To manage patients who undergo mammaplasty with the sympathy and the empathy that they deserve requires an understanding of the multiple and complex meanings of the breast to these patients. I shall try to cover this area first, to provide background for the decision-making process and advice to the patients.

Understanding the Patient

It is in the field of breast augmentation that we can gain an understanding of the importance of this organ to women. Contrary to popular belief, the average woman seeking breast augmentation is not a young single woman who wishes to become a show girl, or a divorcee who is trying to have the operation to help find a new boyfriend or husband. It is usually an educated, upper middle-class, happily married mother with children who has considered the surgery for many years and wants the operation for her own needs. The husband is usually indifferent, although quite supportive of the wishes of his spouse.

The earliest reports on this subject were by Edgerton and colleagues.[1,2] They reported that the woman seeking breast enlargement had feelings of inadequacy about her small breasts and a lower self-esteem and self-confidence than other women. Druss[3] and Baker and associates[4] reported that following augmentation, the patients had more self-confidence, a better image and self-esteem, had ready identification of the implant as part of their body and had a very high level of satisfaction.

However, not until 1977 was a controlled study on the psychological and psychiatric aspects of the patients seeking augmentation reported, by Shipley and associates.[5] They selected first a group of 28 patients who had sought augmentation mammaplasty. Then they selected two separate control groups for comparison from a gynecologic practice, selected by a gynecologist who was not involved in the evaluation of the patients. The first control group comprised 28 women who, in the opinion of the gynecologist, had breasts of average size; these patients served to evaluate the effect of differing *breast size.* The second control was composed of 28 women selected at random who, in the opinion of the gynecologist, had small breasts but who were not seeking augmentation; these patients served to evaluate the effect of differing *motivation.* Table I shows that these patients had similar basic characteristics. In the evaluation of the Ziller Social Self-esteem Test, the authors found that women in the augmentation group (AUG) scored higher but admitted to greater self-consciousness about their bodies than the

Table I—Comparison of Patients Seeking Augmentation and Control Groups*

Background	Seeking augmentation (n = 28)	Control groups: Average breast† (n = 28)	Control groups: Small breast‡ (n = 28)
Average age, yr	31	39	33
Married, %	64	61	57
Mean no. of children	2.7	2.9	2.7
Income, $	16 000	16 000	17 000

*After Shipley and associates.[5]
†To evaluate effect of differing breast size.
‡To evaluate effect of differing motivation.

average-breast control (ABC) patients and the small-breast control (SBC) women. This was in agreement with the previous reports by Edgerton[1,2] in that those in the AUG group were generally attractive and aware of their attractiveness, but nevertheless were self-conscious about the small size of their breasts. More importantly, however, the Attitude Towards Women Scores and the California Psychological Inventory Scores indicated that patients in the AUG and ABC groups had similar personalities, whereas the SBC patients were more liberal, "feminist", independent, cognitively resourceful and intellectually oriented. The authors concluded that "In contrast to the previous uncontrolled studies. . . mammaplasty women scored as psychologically healthy and they were comparable to the average breast size controls with whom they seek physical identification."[5] The SBC group was statistically the most different.

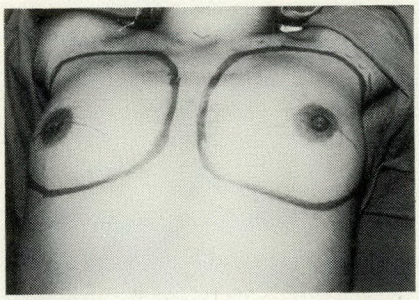


Fig. 1a

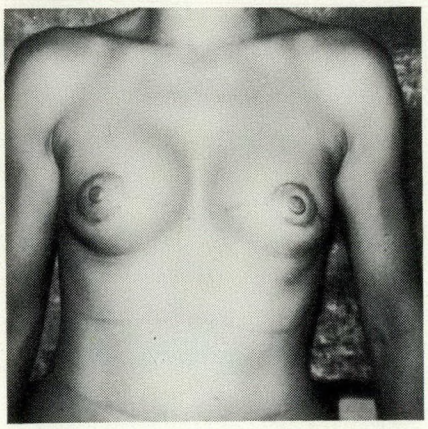


Fig. 1b

FIG. 1—(a) Patient with multiple fibrocystic masses referred by general surgeon for removal of breasts. (b) Using transverse incisions over dome, total mastectomy was performed in subcutaneous plane leaving very thin layer of skin and subcutaneous tissue. Prosthesis was placed underneath pectoralis major muscle in large pocket that included dissection under serratus anterior muscle.

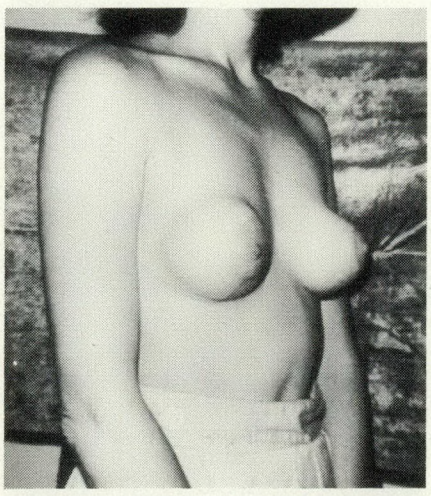


FIG. 2—"Hemispheric dome" deformity seen when fibrous tissues of healed surgical plane contracted around breast prosthesis placed in subcutaneous pocket.

In a later study, Hetter[6] found that women seeking augmentation mammaplasty identified with "feminine women", had a positive body image and a greater interest in styles and fashion than the average woman. Marcia Goin[7] pointed out in her book that "the breast, while consciously representing sexuality and womanly attractiveness to adults, unconsciously really represents the mother". This statement is based on the work of Sigmund Freud[8] in which he pointed out that the mother's breast is the first "object" that the infant experiences in the awareness of the existence of others; as the infant grows emotionally and psychologically, the breast, which was only a part of the mother, is now completed into the "total person" of the mother. All this and the importance that our society has placed on the beautification of the breast in art and advertising have led to the prominence of the breast in representing womanliness and femininity.

Women at High Risk

To paraphrase Dr. Mayo, "It is the right of every woman to want to look normal." To achieve this, we must be able to advise our patients on the proper medical care for diseases and lesions of the breasts, while at the same time be aware of the importance of reconstruction. The previous speakers in this symposium have already provided the data and documented the number of publications that have reported lesions and other factors pointing to the patients who are at high risk for breast cancer. In general, they are women who have a particular family history of breast cancer. The patient who has had cancer in one breast runs a higher risk of having cancer in the opposite breast and patients with severe fibrocystic disease also have a higher incidence of breast cancer than the general population.

The subject of familial breast cancer is beginning to receive more attention. In 1980, Lynch and colleagues[9] found that approximately 20% of the 75 consecutive women with breast cancer whom they evaluated had a family history of breast cancer. Characteristically, these patients have breast cancer of early onset (i.e., in the third or fourth decade of life). Lynch and associates used several of these patients, whose families were in various stages of the cancer genetic evaluation, to illustrate a hypothetical cancer pedigree that was compatible with what was customarily observed in families with autosomal dominant, inherited disorders. They postulated that the early onset of breast cancer in these cases may be a genetic mutation; approximately one half of the female descendants of a gene carrier may be similarly affected. These types of genetic evaluation are essential for our better understanding of the increasingly frequent occurrence of breast cancers of early onset. It is also essential that we have verification, if these findings are valid, from other centres as well.

Indications for Prophylactic Mastectomy

Prophylactic mastectomy now appears to be indicated in patients with lobular carcinoma in situ, intraductal carcinoma, cancer of the breast in the immediate family or chronic fibrocystic disease of the breast with multiple lesions in a given patient, or multiple previous biopsies with persistent breast cysts, or both. The last group presents a difficult problem for the general surgeon in trying to determine which cyst should be biopsied next. Mammography becomes very difficult because of the multiple cysts; thus, one potential treatment is prophylactic mastectomy.

The Procedure

In general, these patients can be treated with either a simple mastectomy or a subcutaneous mastectomy in which the skin over the breast is preserved with or without the nipple areola (Fig. 1). The thinnest possible layer of breast skin is preserved so that not only is the breast gland removed but as much of the subcutaneous tissue as possible between the overlying skin and the gland. This is done because it is very difficult to know where the breast gland begins or ends since it is not an encapsulated organ. The mound is best reconstructed with a Silastic breast prosthesis. The prosthesis used to be placed over the pectoralis major muscle and underneath the skin. However, subsequent scarring resulted in capsular contracture deformities in approximately 80% of these patients (Fig. 2).

Our experience with breast reconstructions following simple or modified radical mastectomies demonstrated that the placement of the silicone prosthesis behind the pectoralis major muscle decreased the degree of capsular contracture and allowed for a more gradual contour on the chest wall that made the result

infinitely better. For that reason better cosmetic results are achieved when the prosthesis is placed behind the pectoralis major and serratus anterior muscles.

Subcutaneous mastectomy can also be performed in patients with a strong family history of breast cancer (Fig. 3). Occasionally, patients with very large breasts seek prophylactic mastectomy and this presents a greater problem. In these cases, the operation is often a simple mastectomy with reconstruction of the breast mounds using portions of the breast skin (Fig. 4). Indeed, the most difficult patients are those with asymmetry. For them a combination of subcutaneous mastectomy and a mastopexy may provide symmetry.

Finally, patients with intraductal carcinoma can be treated with bilateral simple mastectomy with immediate reconstruction (Fig. 5). The nipple areola should be removed and reconstructed with local tissue and skin grafts when the scar around the prosthesis has matured and the dome is properly positioned.

Discussion

An important issue in the discussion of prophylactic mastectomy is the amount of breast tissue that is removed. Although we remove as much of the breast tissue and subcutaneous fat as we can without devascularizing the overlying skin, it is not possible to perform a true complete mastectomy. Goldman and Goldwyn[10] demonstrated in subcutaneous mastectomies performed on cadaver specimens that samples of the fat taken from the breast skin occasionally showed microscopic areas of breast tissue remaining. We estimate that at best we remove 90% to 95% of the breast tissue. However, even in a simple mastectomy, it is unlikely that the mastectomy is complete. Microscopic amounts of breast tissue are left behind in the infraclavicular area as well as in the axillary tail of Spence; perhaps at best 95% to 98% of the breast tissue is removed with this technique. Even with a radical mastectomy where the chest skin is removed and may require a skin graft, at best 98% to 99% is being removed. The issue at hand is not whether 98% is better than 95% which is better than 90%, but whether or not the microscopic tissue that is left behind will undergo transformation to malignant tissue.

I contend that breast cancer develops from within the gland, and grows to the surface to involve the overlying skin only in advanced cases, rather than beginning as cancer in the breast tissue underlying the subcutaneous layer of the skin. If that is correct, then it is unlikely that cancer will develop in the remnant microscopic breast tissue. The opposite could also be true: that the small amount of breast tissue remaining "will take the onslaught" of the circulating hormones; however, there is no evidence that this is the mechanism of the development of breast cancer. If we are to assume that the earliest breast cancer that can be detected weighs 1 g, and 1 g of tissue in the body contains 10^9 cells, we can see that it takes approximately 30 doubling times to reach this number of cells from one original malignant cell. Sparks[11] has pointed out that the doubling time of breast cancer tissue cultures varies tremendously: from 23 to 209 days. If this is the case, it will take between 2 and 17 years before the 30 doubling times are achieved to make the earliest detection of a malignant tumour at 1 g. This appears to be the most logical explanation for the development of breast cancer, and if it is correct, the performance of subcutaneous mastectomy should lead to a decreased incidence. However, only long-term follow-up of these patients will be able to tell whether or not this is indeed correct.

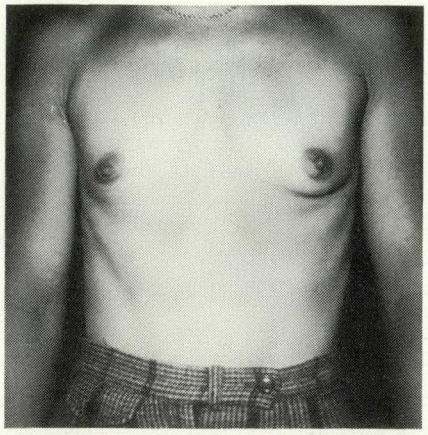


Fig. 3a

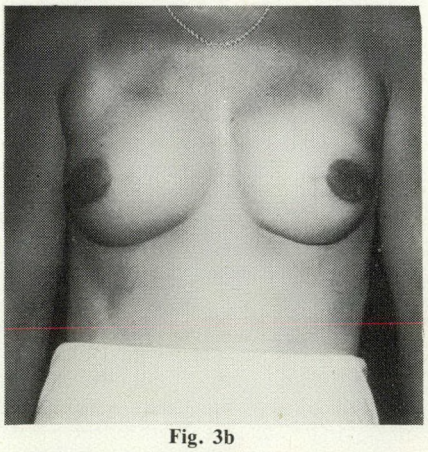


Fig. 3b

FIG. 3—(a) Preoperative appearance of breast of married woman, 32 years old with family history of breast cancer, who desired subcutaneous mastectomy because she wished to have children and was concerned about effects of hormonal stimulation on her breast tissue during pregnancy. (b) Appearance 4 years after operation. Patient has had two children and does not wish to have nipples reconstructed although this has been offered.

Another question is whether the nipple-areola complex should be removed with the gland. In one study by Parry and associates,[12] 250 breasts that were removed because of invasive breast cancer were thoroughly examined by multiple sections. Histologic evidence of nipple involvement was found in 16 cases, 14 of which were determined clinically before operation to be involved; only 2 cases were found histologically without clinical evidence preoperatively (Table II). It appears, therefore, that areolar involvement is uncommon in the absence of clinical manifestation and proximity of the primary tumour to the nipple areola.

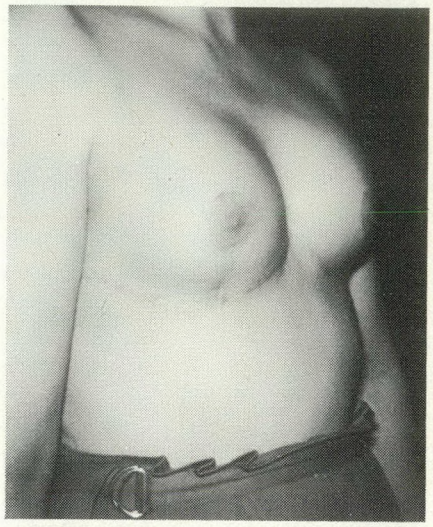


FIG. 4—Postoperative view of breasts of woman in mid-30s who had multiple fibrocystic masses of both breasts. Her 48-year-old sister had undergone mastectomy for invasive cancer. Patient was treated by bilateral total mastectomy, with prostheses placed behind pectoralis major muscle. Dome of mounds was de-epithelialized and skin grafts were used for nipple and areolar reconstruction.

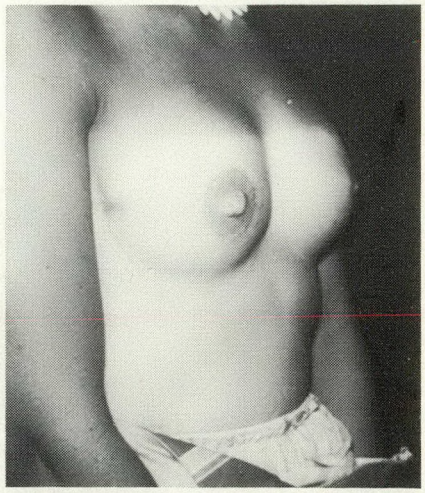
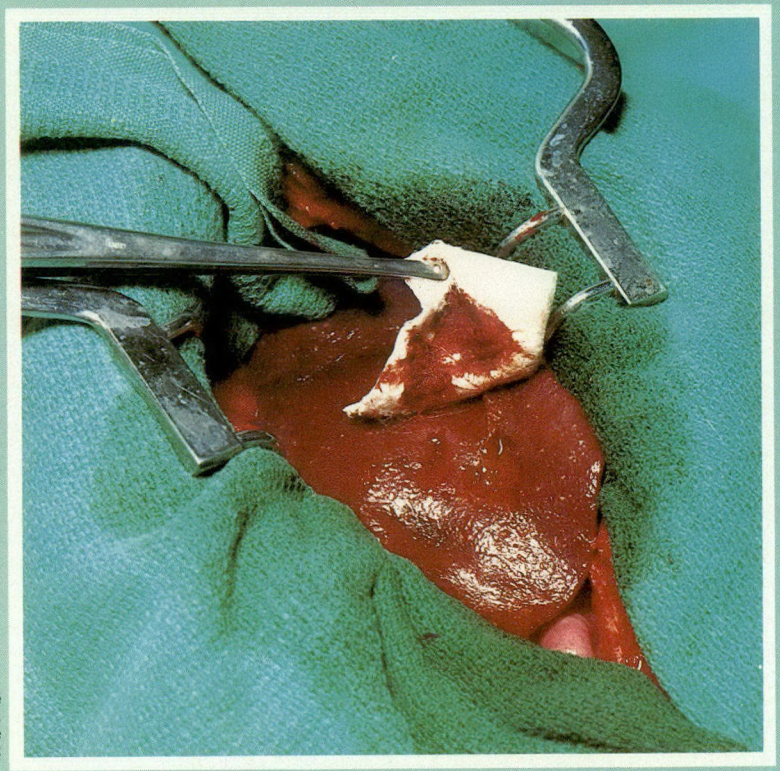


FIG. 5—Postoperative appearance of patient with intraductal carcinoma proven by incisional biopsy. She was treated by bilateral simple mastectomy and immediate reconstruction of mounds. Following maturation of scar tissue around operative site, nipples and areolas were reconstructed using local tissue for nipple and thigh skin grafts for areola.

mallitene®

Microfibrillar Collagen Hemostat



Photograph courtesy of the
University of Alberta,
Surgical Medical Research Institute
Special thanks to Dr. Garth Warnock

In cases where surgical techniques are ineffective in controlling bleeding, surgeons are switching to Mallitene because of its remarkable easy-to-handle form and extremely fast hemostatic action.

MALLITENE
is available in the following sizes:

Size	Weight	Pieces/Pack	Order #
5 x 8 cm	1000 mg.	10	11158
3 x 5 cm	375 mg.	10	11135

Detailed information available on request.

If you would like to try Mallitene, please write us:

malliner laboratories
10548 - 82 Avenue, Edmonton, Alberta T6E 2A4
or CALL US COLLECT
(403) 433-8466

Malliner Laboratories Inc. is a Canadian company wholly owned by Canadians.

Nevertheless, if there is any question, the nipple or areola, or both, should be removed with the breast since both can be reconstructed.

Data are now accumulating on patients treated by subcutaneous mastectomy. Pennisi and Capozzi[13] in 1975 reported on 1385 patients treated by 50 surgeons; they reported 82 cases of occult carcinoma (6% incidental finding of malignant cells within the breast tissue). They also reported that carcinoma developed subsequently in 0.5% of 4179 patients. In 1979, Pennisi[14] reported an incidence of 0.1% among 1000 subcutaneous mastectomies and in 1983 Woods[15] reported a 0.2% rate among 900 patients.

Subcutaneous mastectomy has been criticized by those who believe it is not "prophylaxis". The severest critic has been Louren J. Humphrey who wrote in an editorial[16] that standards of surgical care "must. . . be developed from knowledge of numbers, from critical analyses of studies, and not from arguments based on opinions or some quixotic use of invalid data". Nevertheless, he based the strength of his argument on a personal communication with Dr. Jerome Urban who related his experience on a panel discussion on prophylactic mastectomy held in New York City in 1982 by the American Society of Plastic and Reconstructive Surgeons. Reportedly, Dr. Urban had asked for a show of hands of surgeons in the audience who had experienced the appearance of cancer in a patient who had previously undergone subcutaneous mastectomy, and that Dr. Urban told him that "at least 90 to 100 hands were raised (personal communication)".[16] Unfortunately, Dr. Humphrey's arguments are also not based on numbers.

Indeed, it will take an experience of 10 to 20 years to be able to determine whether or not the incidence of breast cancer following subcutaneous mastectomy is reduced in comparison with that in the normal population. Currently, the likelihood of a young woman suffering from breast cancer in her lifetime is 9%.[17] Women who undergo subcutaneous mastectomy are those who are considered to run a greater than 9% risk of having breast cancer. The reported data to date, an experience between 5 to 10 years, indicates that the incidence of breast cancer after prophylactic subcutaneous mastectomy is less than 0.5%.[13-15] Further collection of data will be able to substantiate whether or not the incidence is kept low following subcutaneous mastectomy. Indeed, until this information is fully available, we cannot consider subcutaneous mastectomy to be truly "prophylaxis".

Table II—Nipple Involvement in 200 Cases of Breast Cancer*

Findings	No. of patients
Nipple involvement	16
Clinical observation preop	
Ulceration	4
Retraction	5
Fixation	5
Negative	2

*From Parry, Cochran and Wolfort.[12]

References

1. EDGERTON MT, MCCLARY AR: Augmentation mammaplasty; psychiatric implications and surgical indications; (with special reference to the use of the polyvinyl alcohol sponge Ivalon). *Plast Reconstr Surg* 1958; 21: 279–305

2. EDGERTON MT, MEYER E, JACOBSON WE: Augmentation mammaplasty. II. Further surgical and psychiatric evaluation. *Plast Reconstr Surg* 1961; 27: 279–302

3. DRUSS RG: Changes in body image following augmentation breast surgery. *J Psychoanal Psychother* 1973; 2: 248–56

4. BAKER JL JR, KOLIN IS, BARTLETT ES: Psychosexual dynamics of patients undergoing mammary augmentation. *Plast Reconstr Surg* 1974; 53: 652–9

5. SHIPLEY RH, O'DONNELL JM, BADER KF: Personality characteristics of women seeking breast augmentation. Comparison to small-busted and average-busted controls. *Plast Reconstr Surg* 1977; 60: 369–76

6. HETTER GP: Satisfactions and dissatisfactions of patients with augmentation mammaplasty. *Plast Reconstr Surg* 1979; 64: 151–5

7. GOIN JM, GOIN MK: *Changing the Body: Psychological Effects of Plastic Surgery,* Williams & Wilkins, Baltimore, 1981

8. FREUD S: *An Outline of Psychoanalysis,* authorized translation by James Strachey, Norton, New York, 1949: 89

9. LYNCH HT, ALBANO WA, LYNCH JF: Genetic counseling, familial breast cancer, and the surgeon's responsibility. *Plast Reconstr Surg* 1980; 66: 303–10

10. GOLDMAN LD, GOLDWYN RM: Some anatomical considerations of subcutaneous mastectomy. *Plast Reconstr Surg* 1973; 51: 501–5

11. SPARKS FC: Current trends in surgery for breast cancer. *Conn Med* 1978; 42: 629–33

12. PARRY RG, COCHRAN TC JR, WOLFORT FG: When is there nipple involvement in carcinoma of the breast? *Plast Reconstr Surg* 1977; 59: 535–7

13. PENNISI VR, CAPOZZI A: The incidence of obscure carcinoma in subcutaneous mastectomy. Results of a national survey. *Plast Reconstr Surg* 1975; 56: 9–12

14. PENNISI VR: Alternatives to subcutaneous mastectomy. Commentary. *Plast Reconstr Surg* 1979; 64: 402–3

15. WOODS JE: Subcutaneous mastectomy: current state of the art. *Ann Plast Surg* 1983; 11: 541–50

16. HUMPHREY LJ: Subcutaneous mastectomy is not a prophylaxis against carcinoma of the breast: opinion or knowledge?(E) *Am J Surg* 1983; 145: 311-2

17. SEIDMAN H, MUSHINSKI MH, GELB SK, SILVERBERG E: Probabilities of eventually developing or dying of cancer — United States, 1985. *CA* 1985; 35: 36–56

Chairman's Comments

Two types of data have been discussed in this symposium. First, scientific observations on the incidence and definition of these diseases have been presented and second, there has been discussion about the interpretation of some of these statistics.

It seems clear from the discussions of Drs. Schechter and Wolmark that some lesions can be categorized pathologically with respect to risk of frank carcinoma developing. These data, when compared to the established statistical risk for the average woman, give us a yardstick by which to make judgements. When we move to the area of intervention, we leave the security of statistical reliability and enter the uncertainty of interpretation, opinion and bias.

Dr. Ariyan has demonstrated the feasibility of reconstructive surgery following mastectomy. The technique seems to be established for prophylactic or therapeutic mastectomy and for the subcutaneous or total versions. However, the intervention has been extended to women with ordinary fibrocystic disease — a type not normally associated with higher cancer risk; it is even suggested in some cases for women with multiple simple cysts whose management is difficult in terms of recurrence. Do all these clinical problems require a solution that seems to be radical?

When all these statistics and opinions are presented to an experienced clinical surgeon, it becomes very difficult to formulate concrete proposals. Dr. Ketcham (see editorial in this issue, pages 194 and 195) prefers to allow the patient a key role in the decision. He thinks that sufficient evidence is lacking to conclude that any of these lesions are precancerous, and he would like to obtain more scientific information through follow-up, in order to acquire a better base for decision-making in the absence of reliable information. We cannot expect patients to make better medical decisions than doctors, so that, for the present, the patient's decisions become choices based on personal preference rather than scientific conclusions.

The essence of the problem for clinicians is that little clinical information exists. The large number of cases compiled by Pennisi and Woods (cited by Ariyan) are a pot-pourri of diagnoses ranging from minimal cancer and precancerous lesions to benign fibrocystic disease, painful cystic change, family histories of uncertain risk and even cancer phobia. Without an adequate definition of the denominator, one cannot expect the numerator to give a reliable indication of the probability of cancer being prevented. Thus, the fact that few cancers appear in the follow-up years doesn't necessarily mean that the operation is preventing cancer. We don't know how many of those patients would have invasive cancer without the operation.

This symposium has indicated that women with intraductal cancer, and to a certain extent those with lobular carcinoma in situ, run an increased risk of having invasive cancer. Applying other risk factors can help define subgroups of patients who are at yet higher risk for future cancer development. Dr. Schechter suggests that this technique may help identify a smaller subgroup of patients in whom 80% of the potential cancers will occur. For the present, this seems to be the best lead we have towards a rational application of this procedure.

Although it can be assumed that total bilateral mastectomy can prevent cancer, it is not yet possible to predict which women are at high enough risk and we cannot achieve consensus on recommending this operation. There is even more uncertainty about relying on subcutaneous mastectomies instead of total mastectomies. Finally, there is an unresolved controversy about the need to consider, for prevention, surgery that is more extreme than one would actually recommend for treatment of invasive ductal cancer. Although prospective controlled studies would obviously contribute to our understanding, none are at present on the horizon.

RICHARD G. MARGOLESE, MD, FRCSC

Symposium chairman

Department of Surgery,
Sir Mortimer B. Davis-
Jewish General Hospital,
Montreal, PQ
H3T 1E2

NOTICES

continued from page 255

Cardiovascular Surgery will be held Nov. 17–21, 1985, in Bangkok, Thailand. The meeting is sponsored by the Association of Thoracic and Cardiovascular Surgeons of Asia, hosted by the Society of Thoracic and Cardiovascular Surgeons of Thailand and supported by the Royal College of Surgeons of Thailand, the Heart Association of Thailand and Chulalongkorn University. English will be the official language for the congress, which will include guest speakers, plenary sessions, symposia, scientific films and exhibits.

Information concerning the congress and travel arrangements can be obtained from Interport, Ltd., PO Box 338, Sunset Beach, CA 90742; (213) 592-4446; Telex 910-380-5385 (Interport SSBH).

Breast and Endocrine Surgery

The Department of Surgery of the University of Minnesota Medical School is holding its 49th Annual Surgery Course, June 24-26, 1985, at Willey Hall, University of Minnesota, Minneapolis, Minn. The major topic of the course will be breast and endocrine surgery. The registration fee is $400 (1200 for residents) and accreditation will be 22 hours in AMA Category 1.

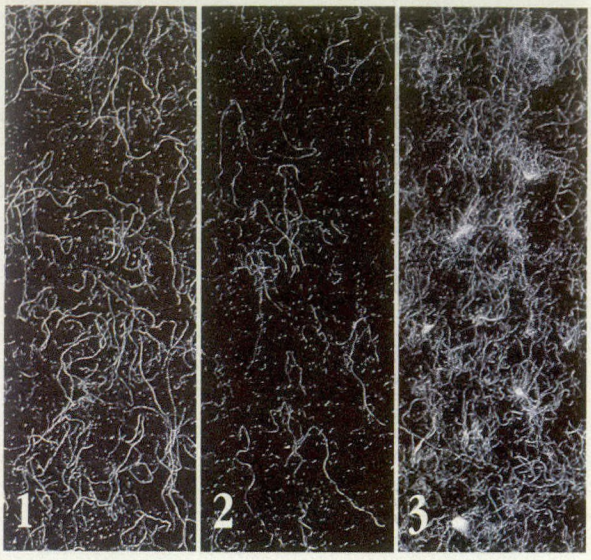
For more information contact: the Office of Continuing Medical Education, University of Minnesota, Box 293, 420 Delaware St. SE, Minneapolis, MN 55455; (612) 373-8012.

American Association for Hand Surgery

The 15th annual meeting of the American Association for Hand Surgery will be held Oct. 24-27, 1985 at the Vista International Hotel, Kansas City, Missouri.

For further information contact: Myra Josephson, Central Office Manager, American Association for Hand Surgery, Ste. 218, 2934 Fish Hatchery Rd., Madison, WI 53713; (608) 272-8940.

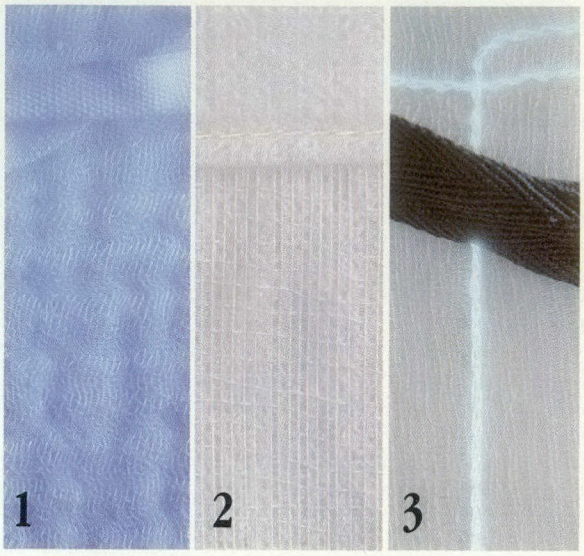
Ask for lint-free



1. *Rewashed laparotomy sponge*
2. *RAY-TEC* disposable laparotomy sponge*
3. *Imported disposable laparotomy sponge*

Every time a laparotomy sponge is laundered, lint content increases. Lint has been shown to cause adhesions due to granulomas.[1,2]

Ask for dye-free



1. *Optical brighteners in rewashed laparotomy sponge*
2. *No optical brighteners in RAY-TEC* disposable laparotomy sponge*
3. *Optical brighteners in imported disposable laparotomy sponge*

Optical brighteners found in most disposable laparotomy sponges or picked up from detergents during laundering are suspected of affecting wound healing.[3]

Ask for RAY-TEC* x-ray detectable laparotomy sponges

- *virtually lint free*
- *no optical brighteners and dye*
- *softer, whiter*
- *longer, softer and absorbent new tab*
- *guaranteed aseptic presentation*

Yours for the asking

RAY-TEC* x-ray detectable disposable laparotomy sponges are totally Canadian made

1. Sturdy BG: Surgical Sponges: A cause of granulomas and adhesion formation. Ann. Surgery 165: 128-134, 1967.
2. Ellis: The cause and prevention of post-operative intraperitoneal adhesions. Surg. Gyn. & Ob. 133: 497-511, 1971.
3. Baron H: The Danger from a Surgical Point of View of Optical Brighteners used in Laundering, Klinik der Medizin, Akademie zu Dusseldorf. Translation from the German Sonderdruck: Stadtehygiene 1/1957.

compresses de laparotomie
discernables aux rayons X

RAY-TEC*

x-ray detectable*
laparotomy sponges

Johnson & Johnson INC.

G. STRINGEL, MD, FRCSC;* N. ANDERSON, MD;* D. MARTIN, MD†

Splenic Abscess

Abscess of the spleen is a rare entity. It may develop after generalized infection, hematologic disorders and trauma. The authors report the case of a 7-year-old boy who presented with a 2-month history of spiking fever, anorexia, fatigue and weight loss. He had left subcostal tenderness and a palpable spleen. He had a history of trauma to the left flank 5 months before admission but a splenic scan obtained at that time appeared normal. A splenic abscess was diagnosed by gallium scanning, computerized tomography and ultrasonography.

Although splenectomy has been advocated as the treatment of choice for splenic abscess, this patient was treated successfully with appropriate antibiotics and simple drainage, preserving the spleen. Cultures grew *Staphylococcus aureus*. Of all the diagnostic methods available, ultrasonography is the least invasive study that will make the diagnosis and is less expensive than some methods.

L'abcès splénique est rare. Il peut survenir à la suite d'une infection généralisée, d'un problème hématologique ou d'un traumatisme. Les auteurs décrivent le cas d'un garçon de 7 ans qui fut hospitalisé souffrant des clochers thermiques, d'anorexie, de fatigue et de perte de poids. Il présentait une douleur sous-costale gauche et sa rate était palpable. On relevait des antécédents de contusion au côté gauche subi 5 mois avant l'entrée à l'hôpital mais une scintigraphie splénique pratiquée à ce moment avait semblé normale. Un abcès splénique fut diagnostiqué par scintigraphie au gallium, tomographie axiale par ordinateur et échographie ultrasonique.

Bien que la splénectomie ait été préconisée comme traitement de choix de l'abcès splénique, le patient fut traité avec succès par antibiothérapie appropriée et simple drainage, avec conservation de la rate. Les cultures révélèrent du *Staphylococcus aureus*. De tous les moyens diagnostiques disponibles, l'échographie ultrasonique est le moins envahissant et il est moins coûteux que certaines méthodes.

Splenic abscess, although it has long been recognized, is a rare condition. It may develop after generalized infection, hematologic disorders or trauma.[1-3] The overall mortality is about 39%, ranging from 15% to 100%.[1-3]

We report the case of a child with a splenic abscess, accurately diagnosed by gallium scanning, computerized tomography and ultrasonography, who was successfully treated by drainage and antibiotic therapy, thereby preserving the spleen.

Case Report

A 7-year-old boy was admitted with a 2-month history of spiking fever, anorexia, fatigue and weight loss of 1.4 kg. Two days before admission a cough developed associated with vomiting. He appeared chronically ill, pale and tired. His temperature was 39.4°C and pulse 124 beats/min. He had moderate left subcostal tenderness and a palpable spleen.

He had been born with a cervical meningocele, which was successfully repaired but required a ventriculoperitoneal shunt. At 1 year of age, he had a *Staphylococcus aureus* infection of the shunt, requiring removal and antibiotic treatment; reinsertion of the shunt was not necessary. Five months before admission he injured his left side in a fall. He suffered left shoulder-tip pain, which subsided rapidly. He was examined at the hospital but no other problem was found. Because of splenomegaly, splenic scanning was done. This did not show rupture; he was thought to have a "mononucleosis-like illness", although his mononucleosis spot test gave negative results. He remained asymptomatic for 2 months.

On admission, his leukocyte count was 19.5 $\times$ 10^9/L with 83% polymorphonuclear leukocytes. The hemoglobin level was 97 g/L, the erythrocyte sedimentation rate was 58 mm/h and mononucleosis spot test gave negative results. The bone marrow was very active and cellular with increased plasma cells. Serum electrolyte levels and results of liver function tests were normal; protein electrophoresis showed elevated levels of α_1 and α_2 globulins; the immunoglobulin A level was also elevated. Blood and urine cultures did not grow any organisms. *Haemophilus influenzae* was isolated from the tracheal aspirate and beta hemolytic streptococcus from a throat swab.

The chest roentgenogram showed an infiltrate in the lower lobe of the left lung; plain abdominal films were not helpful.

Liver-spleen scanning showed splenomegaly (Fig. 1). Gallium scanning demonstrated intense focal uptake in the spleen (Fig. 2), and computerized tomography (Fig. 3) and ultrasonography (Fig. 4) showed a collection of fluid with solid elements along the superior medial aspect of the spleen that was considered to be subcapsular.

A large splenic abscess was drained of 200 mL of pus through a left subcostal incision. Because the abscess was confined to the left upper quadrant of the abdomen and sealed by omentum, care was taken not to contaminate the peritoneal cavity; two large Penrose drains were inserted. Cultures grew *S. aureus* resistant to ampicillin and penicillin but sensitive to cloxacillin, cefamandole and clindamycin.

FIG. 1—Liver and spleen scanning with technetium 99m (left posterior view) shows splenomegaly and displacement of spleen.

*From the *Department of Surgery and †Department of Radiology, Children's Hospital of Eastern Ontario, Ottawa, Ont.*

Accepted for publication July 27, 1984

Reprint requests to: Dr. G. Stringel, Department of Surgery, Children's Hospital of Eastern Ontario, 401 Smyth Rd., Ottawa, Ont. K1H 8L1

Preoperatively the boy was treated with ampicillin and clindamycin. Postoperatively he received cefamandole intravenously for 2 weeks and subsequently cloxacillin orally for 2 more weeks. The Penrose drains were gradually removed over a period of 5 days, starting 5 days after his operation.

Postoperatively the boy remained afebrile. His recovery was smooth and he returned home 2 weeks after operation. Ultrasonography 2 weeks and 6 weeks after operation showed gradual resolution of the splenic defect, and a final examination at 3 months gave normal findings. At follow-up 6 months after operation he was asymptomatic.

Discussion

Splenic abscess is a rare condition and most cases occur in adults. In a recent report by Chun and associates,[1] only 27 of 153 patients were under 19 years of age and only 9 were children under 10 years old.

The spleen is a critical line of defence when the host is invaded by blood-borne bacteria; the unique, sophisticated splenic filter, which receives 5% of the blood volume per minute, traps bacteria and particles larger than 2.5 μm which are subsequently eliminated by various mechanisms. The spleen is the main site of clearance of microorganisms when the host has little or no pre-existing antibody and it is where specific immunoglobulin M (IgM antibody) is initially synthesized.[1,4,5]

Although the spleen is frequently in contact with blood-borne bacteria, it rarely becomes infected. This is supported by the rarity of splenic abscesses in clinical practice and the low frequency of splenic abscesses in autopsy series.[1]

Bacteremia is the first requisite for splenic abscess and most likely a functional or anatomical defect is present for the abscess to develop. Several predisposing factors have been recognized, such as infarcts, trauma with hematoma formation and hemoglobinopathies. Another rare cause of splenic abscess is the direct extension of infection from contiguous organs.[1]

In our case, trauma was documented 5 months before admission and although splenic rupture was considered, this was not demonstrated by scanning done 1 week after injury. It is possible that the splenic laceration was too small to be detected by this examination.

The child had also had an *S. aureus* infection in a ventriculoperitoneal shunt at 1 year of age; we are not sure whether this infection played a role in the development of the splenic abscess.

The most common signs and symptoms associated with splenic abscess are fever, abdominal pain, pleuritic chest pain, abdominal tenderness in the left upper quadrant, splenomegaly or a mass palpable in the left subcostal area and leukocytosis. Other common symptoms and signs are weakness, nausea, vomiting, anorexia, cough, diaphoresis, weight loss and altered bowel habit. Auscultatory abnormalities may be present on the left lower side of the chest as well as signs of pleural effusion or consolidation.[1-3]

Chest roentgenography may show a left pleural effusion and consolidation or pneumonic infiltration in the left lower lobe. Plain abdominal films may show a mass in the left upper quadrant or displacement of the gastric shadow, but these findings are not specific.

Ultrasonography, computerized tomography, gallium and ^{99m}Tc liver-spleen scanning and arteriography are specific studies to recognize splenic abscesses.[1-3]

In our case, the best of these methods were ultrasonography (Fig. 4) and computerized tomography (Fig. 3). Both studies demonstrated the abscess and its subcapsular location. Gallium scanning (Fig. 2) showed intense uptake in the area of the spleen but this was not specific for splenic abscess. Liver-spleen scanning (Fig. 1) did not contribute to the diagnosis except to exclude splenic rupture and liver involvement. Arteriography was not done. Our findings confirmed the experience of others[2] who recommended ultrasonography as the least-invasive study that will make the diagnosis and is also one of the less expensive methods.

Streptococcus is the most common organism in splenic abscess followed closely by *S. aureus* (as in our patient), *Salmonella* sp. and other gram-negative bacilli; the presence of pus with sterile culture has also been reported.[1,3]

Splenectomy has been advocated as the treatment of choice for splenic abscess;[1,3] our patient was successfully treated with appropriate antibiotics and simple drainage. We recommend this approach as the initial treatment of choice, especially in children in whom preservation of the spleen is vital, to avoid the dangers of overwhelming postsplenectomy infection that is associated with 50% mortality.[6] Care must be taken not to contaminate the peritoneal cavity. Broad-spectrum antibiotics should be given before operation until the final culture and sensitivity results are obtained. Antibiotics should be continued intravenously for 2 weeks then orally for 2 more weeks. Follow-up ultrasonography should be done at intervals until the defect has resolved.

With the current emphasis on preserving the spleen in blunt abdominal trauma, we should see fewer overwhelming postsplenectomy infections, but the frequency of splenic abscess may increase.

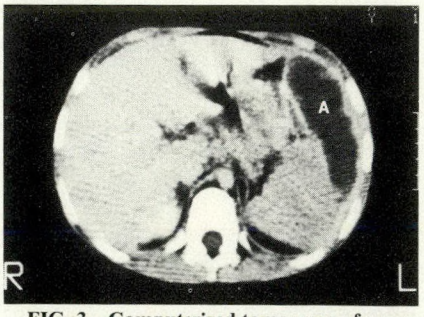


FIG. 3—Computerized tomogram of upper abdomen reveals subcapsular collection of fluid in spleen. A = abscess.

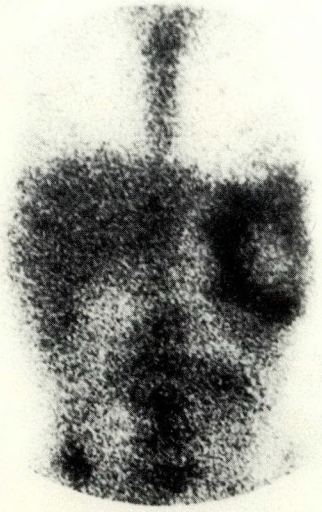


FIG. 2—Gallium scanning shows intense focal uptake in spleen.

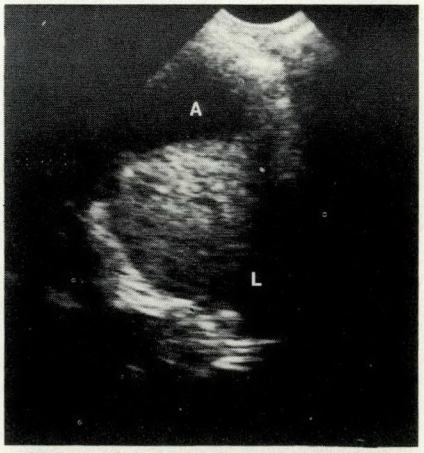


FIG. 4—Transverse ultrasonogram of spleen also demonstrates subcapsular collection of fluid. A = abscess, L = left side.

References

1. CHUN CH, RAFF MJ, CONTRERAS L, VARGHESE R, WATERMAN N, DAFFNER R, MELO JC: Splenic abscess. *Medicine (Baltimore)* 1980; 59: 50–65
2. GRANT E, MERTENS MA, MASCATELLO VJ: Splenic abscess: comparison of four imaging methods. *AJR* 1979; 132: 465–6
3. SIMSON JN: Solitary abscess of the spleen. *Br J Surg* 1980; 67: 106–10
4. EICHNER ER: Splenic function: normal, too much and too little. *Am J Med* 1979; 66: 311–20
5. CLARET I, MORALES L, MONTANER A: Immunological studies in the postsplenectomy syndrome. *J Pediatr Surg* 1975; 10: 59–64
6. KRIVIT W, GIEBINK GS, LEONARD A: Overwhelming postsplenectomy infection. *Surg Clin North Am* 1979; 59: 223–33

continued from page 261

techniques, which in many instances differ from those of other institutions around the world.

Only 165 pages long, the book can easily be read in a single evening. The quality of the colour photographs is excellent and the underlying legends are helpful.

A perusal of this book by junior residents in cardiovascular surgery early in their training program would be very appropriate. This book, therefore, should be in libraries of institutions concerned with training residents in cardiac surgery.

ELLIOT T. GELFAND, MD, FACS, FRCSC

Ste. 550,
8409-112th Street,
Edmonton, Alta.
T6G 1K6

COMPLICATIONS OF FRACTURE MANAGEMENT. Edited by Harry R. Gossling and Stephen L. Pillsbury. 565 pp. Illust. J.B. Lippincott Company, Philadelphia, 1984. $67.50 (US). ISBN 0-397-50584-1.

In the foreword to this book, the point is made that complications of fractures are to be expected given the nature of trauma (e.g., high-velocity injuries), old age, patient's poor state of health and variations of early treatment. Also, complications will arise from treatment or failure of definitive treatment; these complications are avoidable. Generally, this book is directed to those responsible for tertiary care of injured patients.

Andrew Bassett describes in detail current concepts of the physiology of fracture healing, including its bioelectric aspects. This serves as a basis for a general description of his recommended electrical management of ununited fractures. The chapter on management of soft-tissue complications associated with fractures stresses the close mutual relationship now necessary between orthopedic and plastic surgeons, especially since the advent of microsurgery and use of free flaps.

Peter Trafton's thoughtful and beautifully written chapter on infected fractures should be read frequently by orthopedic trainees and at least once a year by every orthopedic surgeon. There is a scholarly study of the theoretical aspects of shock and a detailed discussion of the modern methods of management of shock with no fewer than 263 references.

Neurologic, vascular and pulmonary complications of fractures are adequately discussed in separate chapters. Injury to abdominal organs, and metabolic and gastrointestinal complications receive considered attention. Finally, a chapter on the general complications of fracture management constitutes one third of the book.

Based on an obviously extensive experience with metastatic bone disease, Harrington, in his chapter on the management of pathologic fractures, provides detailed information on the timing and effective use of internal fixation and methylmethacrylate. Salter's clearly written and illustrated chapter on epiphyseal plate injuries reflects the author's extensive knowledge and experience in pediatric orthopedic surgery.

The last 13 chapters are concerned with regions and limb areas. Complications of cervical spine injuries are well detailed with illustrative case reports and excellent roentgenograms. Complications of fractures of the thoracic and lumbar spine are completely discussed, with special reference to the physiology of patients with spinal cord injuries. Stabilization of these fractures with rods and sublaminar wire fixation is surprisingly omitted. Hemorrhagic and urologic complications of sacral and pelvic fractures rightly take precedence over the management of complex pelvic and acetabular fractures by internal or external skeletal fixation. The 10 chapters on fractures affecting specific limb areas are detailed, well edited and contain very few poor reproductions of roentgenograms. The bibliography includes the relevant modern publications and the index is sufficiently detailed to allow this book to be used efficiently as a reference text in orthopedic training centres and by orthopedic and trauma surgeons.

J.P. MOREAU, MD, FACS, FRCSC

Chief of Orthopedic Surgery,
Edmonton General Hospital,
Edmonton, Alta.
T5K 0L4

AN INTRODUCTION TO NEUROSURGERY. 4th ed. Bryan Jennett and Sam Galbraith. 360 pp. Illust. William Heinemann Medical Books Ltd., London; Year Book Medical Publishers, Inc., Chicago, 1983. $49.95. ISBN 0-8151-4869-0.

This small-format text was first published in 1964. The 360 pages of the fourth edition are divided into six sections: intracranial space-occupying lesions, particular intracranial lesions, head injuries, spinal lesions, congenital conditions and lesion-making in the nervous system.

As in past editions, the text is not comprehensive, but rather a "primer" designed to inform the nonspecialist about the recognition, diagnosis and management principles applicable to neurosurgical conditions. Each chapter comprises an orderly progression from the neurologic examination, through differential diagnosis and diagnostic tests to management principles. All these are illustrated by clear, easily comprehensible line drawings and sketches. Suggestions for further reading are included at the end of each chapter. Topical subjects such as brain death, herpetic encephalitis and the management of pain are placed in their proper context. Minor omissions, such as chemonucleolysis, and a personal bias against surgery for brachial neuropathies associated with cervical spondylosis, may be forgiven.

This text is highly recommended for senior medical students, residents rotating on neurosurgical services, neuroscience nurses, and those surgeons located away from neurosurgical centres, who may be called upon occasionally to intervene in neurosurgical cases.

BRIEN G. BENOIT, MD, FACS, FRCSC

Chief, Division of Neurosurgery,
Ottawa Civic Hospital,
1053 Carling Ave.,
Ottawa, Ont.
K1Y 4E9

continued on page 290

D. IAN SOUTTER, MD, FRCSC;* GIAN B. PALOSCHI, MD, FACS, FRCSC;* ROBERT S. PRENTICE, MD, FRCPC†

Pneumatosis Cystoides Intestinalis Simulating Malignant Colonic Obstruction

Pneumatosis cystoides intestinalis is an uncommon condition in which pockets of gas occur intramurally in the gastrointestinal tract. The authors describe the case of a 76-year-old man in whom this condition caused low colonic obstruction, simulating a rectal carcinoma. The patient was successfully treated with high-flow oxygen therapy. This form of therapy has not previously been reported in obstructing lesions, but in this case it successfully relieved the obstruction and thus avoided a colostomy that might have been necessary.

La pneumatose kystique de l'intestin est une maladie rare au cours de laquelle des poches de gaz se forment dans la paroi des voies gastro-intestinales. Les auteurs décrivent le cas d'un homme de 76 ans chez qui cette affection causa une obstruction colique basse simulant un cancer du rectum. Le patient a répondu à un traitement d'oxygénothérapie à haut débit. Cette forme de traitement n'avait pas encore été signalée dans les lésions obstructives mais, dans le présent cas, elle a permis de soulager l'obstruction et, en conséquence, d'éviter une colostomie qui aurait pu s'avérer nécessaire.

Pneumatosis cystoides intestinalis is a relatively rare condition characterized by the presence of multiple intramural pockets of gas in any portion of the gastrointestinal tract and occasionally in the mesenteric attachments.[1] It has been classified as primary (idiopathic) or secondary (coexisting lesion of the gastrointestinal tract) (Table I). About 15% of cases are considered primary; most of these occur in adults and involve the colon, giving rise to the term we have used — pneumatosis coli.

Currently, the pathogenesis of pneumatosis coli is thought to be either mechanical or bacterial.[1-4] The usual clinical presentation is of mild to moderate symptoms of diarrhea, cramping, discharge of mucus and occasional constipation. Hematochezia may occur, and occasionally, be alarming.[5] The findings on abdominal examination are usually unremarkable, although at times the cystic colon may be palpable.[5,6]

We present the case of a patient who had low colonic obstruction that was initially thought to be due to a rectal carcinoma, but proved to be pneumatosis coli.

Case Report

A 76-year-old man, known to have chronic obstructive pulmonary disease, was admitted with a low colonic obstruction. A benign polyp 26 years previously had been managed by a colotomy and polypectomy, and 8 years previously sigmoidoscopic polypectomy was done. Follow-up colonoscopic examination 6 years before revealed no colonic abnormality. His presenting symptoms consisted of 5 days of increasing abdominal distension, generalized abdominal discomfort, absence of bowel movements and very little flatus. Before this he noted a decrease in the calibre of his stool for about 2 weeks. There was no history of diarrhea, mucous discharge, tenesmus or rectal bleeding. He was not a known diabetic. He had recently had an exacerbation of his chronic obstructive pulmonary disease for which his prednisone dosage had been increased from 5 mg twice daily to 60 mg once a day, then decreased to 20 mg daily.

Table I—Gastrointestinal Conditions Associated With Pneumatosis Cystoides Intestinalis*

Peptic ulcer disease
Intestinal obstruction
Postsurgical bowel anastomosis
Mesenteric vascular occlusion
Acute necrotizing enterocolitis
Chronic inflammatory disease (e.g., regional enteritis, ulcerative colitis, tuberculosis)
Perforated diverticula
Collagen disorders (especially scleroderma)
Whipple's disease
Abdominal trauma
Ingestion of caustic agents
Intestinal parasites
Intestinal lymphosarcoma
Intestinal instrumentation

*Modified from Sleisenger and Fordtran.[6]

He was a slightly obese, afebrile, mildly dehydrated man with a blood pressure of 140/80 mm Hg, pulse 76 beats/min and regular. There was no adenopathy, pallor, cyanosis or icterus. The chest was increased in the anteroposterior diameter and he had bilateral expiratory wheezing. There was no jugular venous distension or abnormal heart sounds. The abdomen was distended, soft and nontender with increased bowel sounds. Rectal examination revealed an enlarged prostate as well as a separate mass situated anteriorly about 8 cm from the anal verge. This mass was nodular, firm and covered two thirds of the rectal circumference at its palpable lower margin.

Laboratory findings were as follows: hemoglobin 116 g/L, hematocrit 35.4%, leukocyte count 10.4×10^9/L, serum sodium 138 mmol/L, potassium 4.4 mmol/L, chloride 103 mmol/L and bicarbonate 20.1 mmol/L, blood urea nitrogen 125 mmol/L urea and blood glucose 12.7 mmol/L. Results of arterial blood gas studies on room air were: pH 7.40, partial pressure of oxygen 71.3 mm Hg and partial pressure of carbon dioxide 32.5 mm Hg.

Plain films of the abdomen showed a distended colon, with air and stool from sigmoid to cecum but no gas in the rectum. Parts of the sigmoid colon showed linear streaks of gas within the wall. Roentgenograms after barium enema revealed an area of marked narrowing with shouldering and nodularity and nearly total retrograde obstruction (Fig. 1). We believed that this represented a carcinoma of the rectum with pneumatosis coli proximally.

Clinically, we thought this man had an obstructing malignant rectal carcinoma. During sigmoidoscopic examination, pale grey grape-like clusters were seen projecting circumferentially into the rectal lumen. The diagnosis of pneumatosis coli was made at the time of biopsy when these lesions were seen to collapse. Histologically, there were dilated submucosal spaces showing no evidence of malignant change.

The patient was treated with nasogastric tube

*From the *Department of Surgery and †Department of Pathology, Hôtel Dieu Hospital, Queen's University, Kingston, Ont.*

Accepted for publication July 30, 1984

Reprint requests to: Dr. D. Ian Soutter, 706-25 Wood St., Toronto, Ont. M4Y 2P9

suction, intravenous infusion of crystalloids and 50% oxygen by venturi-mask for 48 hours. Twenty-four hours after initiation of oxygen therapy, he was passing gas and had a small bowel movement. All colonic symptoms resolved and a follow-up roentgenogram after barium enema obtained 6 days later showed resolution of the obstructing cysts (Fig. 2). He was well at 15 months after discharge.

Discussion

This case appeared to fall into the category of primary pneumatosis cystoides intestinalis in that no associated gastrointestinal lesions were noted clinically or pathologically. The rectal biopsy specimens showed dilated submucosal spaces without any recognizable cellular lining, which is the usual histologic appearance of this entity.[1,6]

The association between pneumatosis cystoides intestinalis and chronic obstructive pulmonary disease has often been reported. A suggested mechanism[7-9] begins with rupture of pulmonary blebs into the subpulmonary space; the air then makes its way through the mediastinum and retroperitoneum, eventually reaching the bowel wall via its mesenteric attachments. Our patient had chronic obstructive pulmonary disease, so he may fall into this category.

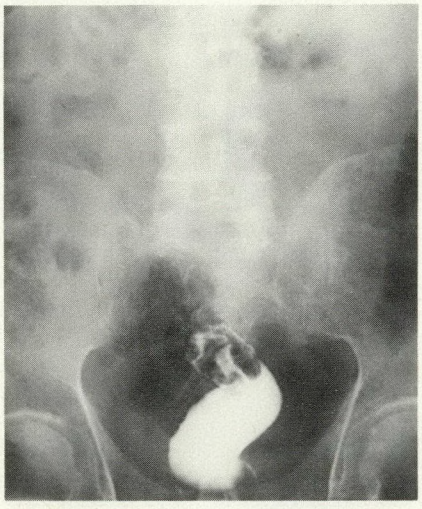


FIG. 1—Roentgenogram after barium enema shows obstructing lesion of distal rectum simulating carcinoma. Proximal gas-filled cysts can be seen.

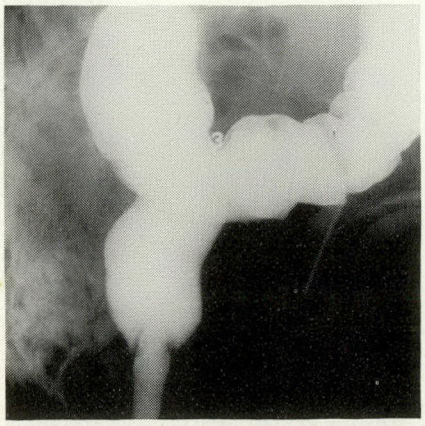


FIG. 2—After treatment with oxygen, obstructing cysts in distal rectum have resolved.

Important complications of pneumatosis cystoides intestinalis are quite unusual. They include pneumoperitoneum,[2,10-15] pneumopericardium,[15] malabsorption[16] and extensive hemorrhage.[5] In addition, obstruction has been associated with pneumatosis cystoides intestinalis in two contexts. The more common is when this condition is secondary to obstructing gastrointestinal lesions such as pyloroduodenal disease,[2,11,17-20] carcinoma,[21] anastomotic stricture,[22] volvulus[2,3,14,18-20,23,24] and intussusception.[15] The proposed mechanism here is that of increased intraluminal pressure secondary to the obstruction, in combination with some form of mucosal disruption, allowing gas to penetrate the intestinal wall and dissect the tissue planes.[2]

The less common occurrence is that of pneumatosis coli causing colonic obstruction as in our case. Meikle[10] reported a case of pneumatosis coli resulting in obstruction, stercoral ulceration and perforation that led to laparotomy. Gillon and associates[3] described two patients in whom they believed pneumatosis coli led to sigmoid volvulus that required operative intervention. Jones and Cole[4] and Paris and Fraire[25] reported cases of small-bowel obstruction secondary to gas cysts involving the small intestine.

High-flow oxygen therapy has been used in the treatment of pneumatosis cystoides intestinalis since 1973[26-28] on the premise that raising arterial oxygen tension to between 200 and 300 mm Hg results in subatmospheric nitrogen pressures in the end-capillary and venous blood, as the oxygen (which displaces much of the nitrogen) is readily utilized by the colonic tissues. The resultant nitrogen-pressure gradient between the cystic spaces and the venous blood promotes collapse of the cysts. High-flow oxygen treatment appears to be widely accepted as being beneficial. It may be required for up to 6 days.[26,27]

The use of oxygen therapy in obstructing lesions due to pneumatosis coli has not previously been reported. Since there is no immediate danger of vascular compromise from the obstructing process, laparotomy is not thought necessary and release of the obstruction should occur when oxygen at a high flow rate is given, as happened in our case. The colonic obstruction was caused by a benign process so oxygen therapy avoided a colostomy that would have been necessary if the obstruction had not resolved otherwise.

References

1. PRIEST RJ, BOCKUS HL (eds): *Gastroenterology, Vol 2,* 3rd ed, Saunders, Philadelphia, 1976: 1097–104
2. ELIDAN J, GIMMON Z, SCHWARTZ A: Pneumoperitoneum induced by pneumatosis cystoides intestinalis associated with volvulus of the stomach. *Am J Gastroenterol* 1980; 74: 189–95
3. GILLON J, HOLT S, SIRCUS W: Pneumatosis coli and sigmoid volvulus: a report of 4 cases. *Br J Surg* 1979; 66: 802–5
4. JONES AW, COLE FM: Intestinal obstruction due to pneumatosis intestinalis. *Postgrad Med J* 1967; 43: 680–2
5. SMITH WG, ANDERSON MJ JR, PEMBERTON HW: Pneumatosis cystoides intestinalis involving the left portion of the colon; report of four cases diagnosed at sigmoidoscopy. *Gastroenterology* 1958; 35: 528–33
6. SLEISENGER MH, FORDTRAN JS: *Gastrointestinal Disease,* 3rd ed, Saunders, Philadelphia, 1983: 1302–7
7. DOUB HP, SHEA JJ: Pneumatosis cystoides intestinalis. *JAMA* 1960; 172: 1238–42
8. KEYTING WS, MCCARVER RR, KOVARIK JL, DAYWITT AL: Pneumatosis intestinalis: a new concept. *Radiology* 1961; 76: 733–41
9. DORSTEN JF: Pneumatosis cystoides intestinalis: report of three cases. *J Am Osteopath Assoc* 1981; 81: 123–31
10. MEIKLE G: A case of pneumatosis coli: pneumatosis cystoides intestinalis of the sigmoid colon causing intestinal obstruction, stercoral ulcer and perforation. *J R Coll Surg Edinb* 1965; 11: 65–7
11. ECKER JA, WILLIAMS RG, CLAY KL: Pneumatosis cystoides intestinalis —bullous emphysema of the intestine. A review of the literature. *Am J Gastroenterol* 1971; 56: 125–36
12. CUTLER D, MALDONADO P, GARCIA-LUNA J: Pneumatosis cystoides intestinalis. Report of 22 cases. *Am J Proctol* 1969; 20: 261–8
13. BROECKER BH, MOORE EE: Pneumoperitoneum due to pneumatosis cystoides intestinalis in idiopathic megacolon. *JAMA* 1977; 237: 1963
14. JONES JD: Gas cysts of the intestine. *Br J Surg* 1948; 36: 49–50
15. HERRINGTON JL JR: Intestinal bypass enteritis causing pneumoperitoneum, pneumopericardium, and cervical emphysema. *Am Surg* 1982; 48: 279–81
16. YUNICH AM, FRANDKIN NF: Fatal sprue (malabsorption) syndrome secondary to extensive pneumatosis cystoides intestinalis. *Gastroenterology* 1958; 35: 212–7
17. DHALL DP, MAHAFFY RG, MATHESON NA: Intestinal pneumatosis treated by pyloroplasty. *J R Coll Surg Edinb* 1968; 13: 226–9
18. MEYERS MA, GHAHREMANI GG, CLEMENTS JL JR, GOODMAN K: Pneumatosis intestinalis. *Gastrointest Radiol* 1977; 2: 91–105
19. OLMSTEAD WW, MADWELL JE: Pneumatosis cystoides intestinalis: a pathophysiologic explanation of the roentgenongraphic signs. *Gastrointest Radiol* 1976; 1: 177–81
20. KOSS LG: Abdominal gas cysts (pneumatosis cystoides intestinorum hominus): analysis with report of a case and critical review of literature. *AMA Arch Pathol* 1952; 53: 523–49
21. RABIN MS, BLEDIN AG, PRICE HI: Pneumatosis coli secondary to colonic obstruction. A case report. *S Afr Med J* 1978; 53: 1078–9
22. KLEINMAN PL, KING DR: Ischemic jejunitis and pneumatosis intestinalis secondary to anastomotic obstruction following jejunal atresia repair. *Gastrointest Radiol* 1977; 2: 113–5
23. WERTKIN MG, WETCHLER BB, WAYE JD, BROWN LK: Pneumatosis coli associated with sigmoid volvulus and colonoscopy. *Am J Gastroenterol* 1976; 65: 209–14
24. BURN JL, JONES BS: Pneumatosis cystoides intestinalis. *Br Med J* 1961; 2: 747–9
25. PARIS MD, FRAIRE AE: Intestinal obstruction from pneumatosis cystoides intestinalis (C). *JAMA* 1981; 246: 622
26. DOWN RHL, CASTLEDEN WM: Oxygen therapy for pneumatosis coli. *Br Med J* 1975; 1: 493–4
27. FORGACS P, WRIGHT PH, WYATT AP: Treatment of intestinal gas cysts by oxygen breathing. *Lancet* 1973; 1: 579–81
28. BRITTEN-JONES R: A major advance in the management of pneumatosis coli. *Aust NZ J Surg* 1975; 45: 367–71

DENNIS L. MODRY, MD, FRCSC; PHILIP E. OYER, MD, FACS; STUART W. JAMIESON, MB, FRCS; EDWARD B. STINSON, MD, FACS; JOHN C. BALDWIN, MD; BRUCE A. REITZ, MD; KEITH D. DAWKINS, MB; CHRISTOPHER G.A. MCGREGOR, MD; SHARON A. HUNT, MD; MARC MORAN, MD; BRYAN MYERS, MD; NORMAN E. SHUMWAY, MD, PH D, FACS

Cyclosporine in Heart and Heart-Lung Transplantation

At Stanford University Medical Center from January 1968 until January 1984, 288 patients received 313 heart transplants. The immunosuppressive regimen before December 1980 consisted of azathioprine and prednisone, with or without rabbit antithymocyte globulin. After that time cyclosporine replaced azathioprine. In 92 recipients of 95 heart allografts, the 1- and 3-year survival rates were 82% and 65% to 70% respectively. In the 3 years from March 1981 to March 1984, successful heart-lung transplantation was accomplished in 13 of 19 recipients, using cyclosporine-based immunosuppression. Survival ranged from 1 to 38 months.

While it is true that cyclosporine has improved survival in heart transplant recipients, has allowed successful heart-lung transplantation to be performed, has shortened intensive care unit and total hospital stays and therefore hospital costs, and has allowed easier management of rejection and infection, several disconcerting problems have not yet been resolved. These include hypertension that is difficult to control and renal dysfunction in all patients, and the fact that cellular and humoral rejection still occurs, as manifested by graft atherosclerosis, bronchiolitis obliterans and classic acute rejection. Better understanding and application of cyclosporine immunosuppression will undoubtedly minimize both cyclosporine- and non-cyclosporine-related postoperative complications and will improve survival even further.

De janvier 1968 à janvier 1984, 288 patients ont reçu 313 greffes cardiaques au Stanford University Medical Center. Avant décembre 1980, le traitement immunosuppresseur était composé d'azathioprine et de prednisone, associées ou non à de l'immunoglobuline antithymocytaire de lapin. Par la suite, la cyclosporine est venue remplacée l'azathioprine. La survie à 1 et 3 ans chez 92 receveurs de 95 allogreffes cardiaques fut de 82% et de 65% à 70% respectivement. Au cours des 3 années qui se sont écoulées entre mars 1981 et mars 1984, grâce à la cyclosporine, des greffes coeurs-poumons ont été réussies chez 13 des 19 receveurs. La survie va de 1 à 38 mois.

Même s'il est vrai que la cyclosporine a amélioré la survie des greffés cardiaques, rendu possible le succès des greffes coeurs-poumons, réduit le séjour aux soins intensifs, la durée d'hospitalisation et, par conséquent, les coûts, et, finalement, permis d'affronter plus facilement les rejets et les infections, il reste bon nombre de problèmes déroutants à résoudre. Parmi ces complications, on note une hypertension difficile à traiter et une insuffisance rénale affectant tous les patients, et le fait que surviennent encore des réactions de rejet à médiations cellulaire et humorale qui se manifestent par de l'athérosclérose du greffon, une bronchiolite oblitérante et le rejet aigu classique. Une meilleure compréhension de l'immunosuppression à la cyclosporine et une meilleure utilisation de ce médicament permettront sans nul doute de minimiser les complications postopératoires reliées ou non à la cyclosporine, et d'améliorer encore la survie.

From the Department of Cardiovascular Surgery, Stanford University Medical Center, Stanford, Calif.

Accepted for publication Nov. 19, 1984

Reprint requests to: Dr. Dennis L. Modry, Division of Cardiovascular Surgery, University of Alberta Hospitals, 112th Street and 84th Avenue, Edmonton, Alta. T6G 2B7

The introduction in December 1980 at Stanford Medical Center of cyclosporine to suppress the immune response and the gradually improving survival rates of preceding years (Fig. 1) have contributed to the current revival of cardiac transplantation around the world (Fig. 2) and have allowed successful heart-lung transplantation to be performed, with long-term survival.[1,2] To define the current advantages and disadvantages of cyclosporine use, the clinical data from all patients who had transplants and cyclosporine immunosuppression at Stanford University Medical Center between December 1980 and January 1984 are reviewed and compared with the data generated from earlier transplantations when immunosuppression was based on the use of azathioprine, prednisone and antithymocyte globulin of rabbit origin.

Cyclosporine in Heart Transplantation

From Jan. 1, 1968 to Dec. 31, 1983, 313 heart transplantations were performed in 288 patients. At the time of writing, the total number of 1-year survivors was 155 and 121 patients were alive

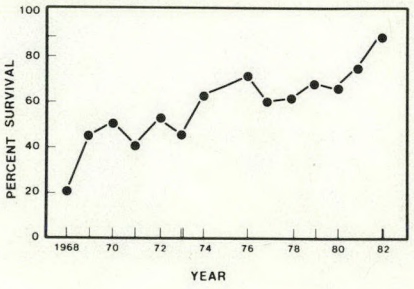


FIG. 1—Progressive improvement in 1-year survival rates of heart transplant recipients at Stanford University Medical Center.

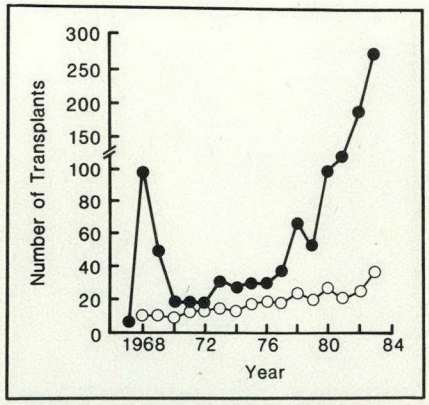


FIG. 2—Total number of heart transplants performed by year. Open circles indicate procedures carried out at Stanford University Medical Center, closed circles are those performed world wide.

1 week to 14 years after transplantation. Nearly 90% of these patients were fully rehabilitated. From December 1980, 92 patients (74 male, 18 female) who received cyclosporine for immunosuppression had 95 transplants. These patients ranged in age from 13 to 52 years. There were six retransplantations.

The preoperative diagnoses included coronary artery disease (36 patients), idiopathic cardiomyopathy (40), viral or familial cardiomyopathy (11), congenital heart disease (3) and others (2).

Survival

To understand best the effect that cyclosporine has had on survival of heart recipients, one can contrast the survival curve generated in these patients with that of two previous immunosuppressive eras and of patients who did not have a transplant (Fig. 3). Of patients selected for transplantation for whom a suitable donor was not available, all died in the first year (mean survival 44 days). From January 1969 until December 1973, the immunosuppressive regimen consisted of azathioprine and prednisone. One- and 5-year survival rates were 42% and 15% respectively. With the introduction of prophylactic rabbit antithymocyte globulin, given in the first few days after transplantation, the 1- and 5-year survival rates increased to 62% and 42% respectively. From December 1980 until December 1983, cyclosporine supplanted azathioprine, resulting in improved graft survival rates to 82% at 1 year and nearly 70% at 3 years. Twenty patients who had cyclosporine for immunosuppression died for the following reasons: rejection 3, infection 8, malignant disease 3, coronary artery disease 2, pulmonary hypertension 1, acute graft failure 1, cerebrovascular accident 1 and cerebral edema 1.

Immunosuppressive Regimen

Immunosuppression consisted of the administration of cyclosporine, 12 to 18 mg/kg, orally, 6 hours before operation. Intraoperatively, after cardiopulmonary bypass was discontinued, 500 mg of methylprednisolone sodium succinate was administered intravenously. Postoperatively, 15 mg of methylprednisolone sodium succinate was given (three doses at 8-hour intervals) and cyclosporine, 12 to 18 mg/kg daily (in equal divided doses every 12 hours). The dose of cyclosporine was tapered gradually over several days to several weeks according to blood levels which were maintained between 100 and 300 ng/mL. On day 1 postoperatively, following the third dose of methylprednisolone, prednisone was begun at a rate of 1 mg/kg daily (in equal divided doses every 12 hours), along with the cyclosporine. The prednisone dose was tapered to 0.8 mg/kg daily by 2 weeks, 0.5 mg/kg by 4 weeks and 0.2 mg/kg by 8 weeks. Rabbit antithymocyte globulin (2.5 mg/kg, intramuscularly, preoperatively and on postoperative days 1 and 2) was given prophylactically to the first 27 patients, but not to the subsequent 65 patients.

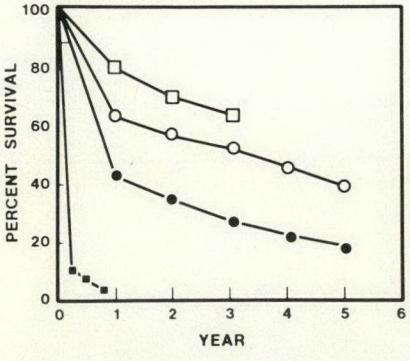


FIG. 3—Survival of patients in three immunosuppressive eras compared with that of patients who did not undergo transplantation. (Open squares = Jan. 1981 to Dec. 1983, open circles = Jan. 1974 to Dec. 1980, black circles = Jan. 1968 to Dec. 1973, black squares = not transplanted.)

Rejection

Diagnosis. —With conventional immunosuppression based on the use of azathioprine, antithymocyte globulin and prednisone, rejection could be suspected by noting a 20% or more decrease in the cumulative voltage of the electrocardiogram (leads I, II, III, V_5 and V_6).[3,4] Similarly, in the face of a markedly shortened half-life of circulating rabbit globulin, or in the presence of a large volume of circulating T lymphocytes, rejection was likely occurring or was imminent.[3] Clinical signs indicative of graft dysfunction were those of congestive heart failure and were late findings. Definite diagnosis could be achieved only with endocardial biopsy when rejection was suspected, using the previously described criteria.[3,4]

Unfortunately, with cyclosporine, the electrocardiogram is not a reliable indicator, circulating T-cell levels are unreliable and clinical findings are absent. Therefore, endocardial biopsy is the only currently reliable means of diagnosing rejection in most instances. Surveillance biopsies, therefore, must be performed weekly for the first 2 to 3 months, then bimonthly up to 6 months and every 3 to 4 months thereafter. The endocardial bioptome is passed percutaneously by the Seldinger technique through the right internal jugular vein and under fluoroscopic control is positioned within the right ventricle; usually three biopsy specimens are taken from the interventricular septum. More than 5000 biopsies have been performed at Stanford University Medical Center with no deaths and only three perforations that required exploration.

Differences in histologic findings between azathioprine- and cyclosporine-treated patients appear to correlate with differences in clinical findings. Fig. 4 illustrates normal myocardium in a biopsy specimen. Acute severe rejection in a patient immunosuppressed with azathioprine and prednisone uniformly is manifested by myocardial edema and lymphocytic infiltration (Fig. 5); this leads to a decrease in electrocardiographic voltage and a decrease in diastolic compliance with the ultimate appearance of S3 or S4 gallop sounds;[3] atrial arrhythmias and variable degrees of heart block often ensue. Congestive heart failure and death secondary to cardiogenic shock rapidly follow if treatment of the rejection is not optimal.

With cyclosporine, severe allograft rejection is not associated with myocardial edema (Fig. 6), hence the rejection is nearly always clinically silent. Recently, two patients who died of acute rejection presented with a low-grade fever, myalgia and weakness. In the first patient, rejection was not suspected, and a biopsy was not performed before his sudden cardiac arrest from which he could not be resuscitated. In the second patient, the severity of rejection seen in the biopsy specimen was not fully appreciated; the patient was undertreated. Although all rejection episodes that occurred in patients during their initial hospital stay were treated with intravenous Solu-Medrol, once patients were discharged subsequent rejection episodes were treated by increasing the prednisone dosage to 100 mg/d for 3 days, then tapering the dosage schedule by 10 mg every other day until the dosage was approximately 10% above the previous maintenance dosage. Currently, for patients who have been discharged from hospital, important rejection episodes associated with cardiac dysfunction or echocardiographic evidence of rejection[5] or important clinical findings are treated with intravenous Solu-Medrol. It is peculiar that the mononuclear infiltrate in patients immunosuppressed with cyclosporine may persist for weeks or months following treatment. In the absence of myocyte necrosis, one can only speculate as to the biologic nature of these cells.

Nearly 25% of patients in the cyclosporine group were free of rejection by postoperative day 60 as opposed to approximately 18% in the azathioprine group.[6] Although this difference was not statistically significant, the severity, as reflected by cardiac dysfunction and death from rejection, was significantly less in patients receiving cyclosporine.[7] This was further reflected by decreased

time spent in the intensive care unit and an overall shorter hospital stay.

Treatment.—Acute rejection during the initial hospital stay is treated with 1000 mg of methylprednisolone sodium succinate, administered intravenously daily for 3 days. The prednisone reduction is interrupted and the dose is held constant. If serum levels of cyclosporine are below the targeted therapeutic range, the oral dose of cyclosporine is increased. Rabbit antithymocyte globulin is used only if extensive myocyte necrosis is noted in the very first cardiac biopsy specimen on postoperative day 7, if rejection with myocyte necrosis is still present following two courses of methylprednisolone sodium succinate and in the presence of life-threatening acute rejection in patients in cardiogenic shock.

Infection

Infection accounted for 40% of all deaths in the cyclosporine-treated transplant recipients as opposed to 66% of the deaths in the azathioprine group. The total number of infectious episodes, however, did not appear to be significantly less than in the azathioprine group in the first 3 years after transplantation (Fig. 7). A trend towards fewer bacterial, fungal and protozoal infections is balanced by an increase in viral infections (mainly trivial mucocutaneous lesions) when cyclosporine is used. As with rejection, the infectious episodes are easier to treat and the hospital stay is shortened; overall, it is likely that a decrease in the severity of infectious episodes with cyclosporine and improved diagnosis and management have contributed to an improvement in survival.

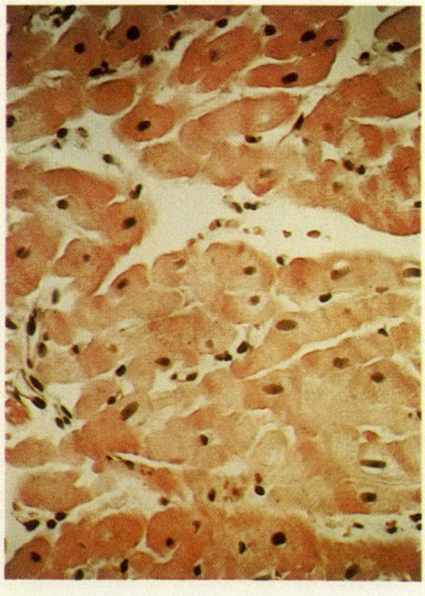


FIG. 4—Normal myocardial biopsy specimen (hematoxylin and eosin, reduced by 53% from × 400).

Malignant Disease

In patients at risk more than 3 years after transplantation who received azathioprine, prednisone and antithymocyte globulin for immunosuppression, 10 lymphomas developed, of which 6 followed primary transplantation in 124 patients (5%) and 4 followed retransplantation in 10 patients (40%). The higher incidence following retransplantation likely reflected the longer period of immunosuppression. Leukemia occurred once after primary transplantation.

From December 1980 until January 1982 the cyclosporine and prednisone immunosuppression was combined with a short prophylactic course of antithymocyte globulin. Five lymphomas occurred after primary transplantation in 27 patients for an incidence of 19%. The apparently synergistic oncogenic effect of antithymocyte globulin and cyclosporine was also noted in primates. Accordingly, from Jan. 1, 1982, the routine prophylactic use of rabbit antithymocyte globulin has been stopped. In 67 patients, only one lymphoma occurred, a rate of 1.5%. Of the six patients with lymphomas, two are alive following local excision and radiotherapy. One patient also received acyclovir. Epstein–Barr virus has been implicated in the pathogenesis of this lymphoproliferative disorder.[8-10]

Coronary Artery Disease

That graft atherosclerosis might be a problem was not recognized initially. The incidence, however, at 3 years was 100%.[3] The generation of graft atherosclerosis was thought to be related to immunologically mediated intimal and endothelial injury, with subsequent deposition of platelets followed by myointimal proliferation. Accordingly, antiplatelet agents combined with warfarin were administered prophylactically. This resulted in a 50% reduction in graft atherosclerosis at 3 years. Since 1979, dipyridamole alone has been used, because, in a subset of patients in whom warfarin could not be administered, the incidence of graft atherosclerosis was the same as in those who had received both warfarin and dipyridamole. One of the purported mechanisms of action of cyclosporine is to inhibit T-cell dependent antibody formation, and it was hoped early on that graft atherosclerosis might be markedly reduced or even eliminated. While the former may still be true, two patients have died of severe graft atherosclerosis and myocardial infarction and a third patient is currently awaiting re-

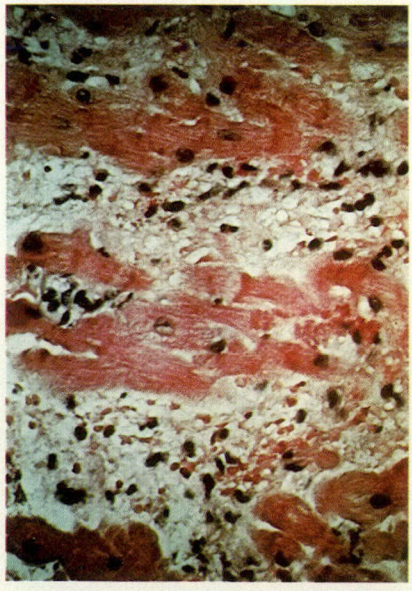


FIG. 5—Myocardial biopsy specimen demonstrates acute severe rejection with marked myocardial edema and mononuclear infiltration in patient given azathioprine and prednisone for immunosuppression (hematoxylin and eosin, reduced by 53% from × 400).

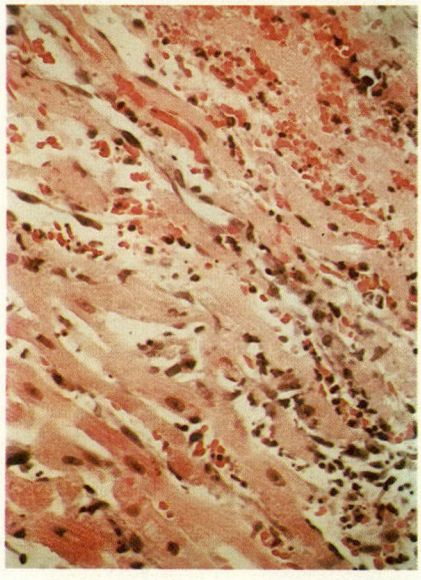


FIG. 6—Myocardial biopsy specimen demonstrates acute severe rejection with myocyte necrosis and mononuclear infiltration but distinct absence of myocardial edema in patient given cyclosporine for immunosuppression (hemotoxylin and eosin, reduced by 53% from × 400).

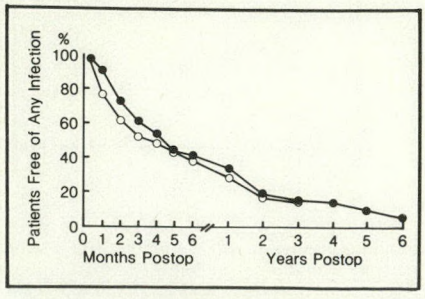


FIG. 7—Total number of infectious episodes is similar in cyclosporine (open circles) and azathioprine (closed circles) groups.

transplantation because of serious myocardial infarction.

Complications Related to the Use of Cyclosporine

Hypertension.—Hypertension in patients immunosuppressed with azathioprine and prednisone was infrequent and tended to occur in older patients with atherosclerotic heart disease. However, with cyclosporine, severe hypertension was invariably present early after operation and required large doses of nitroprusside frequently in combination with trimethaphan and occasionally even boluses of hydralazine. This hypertension is reflected by severe headaches that often develop as the blood pressure increases, and which, therefore, could be controlled by decreasing the blood pressure. Wellands (personal communication, 1983) has reported intracerebral hemorrhage early after operation as a result of uncontrolled hypertension. The mechanism of this hypertension is unclear, but nearly all patients are hypertensive within 2 or 3 months of operation and require a variety of antihypertensive drugs or combination of drugs for its control. There is no single drug or combination, however, that is consistently effective for all patients.

Renal dysfunction.—This has occurred in most patients. There is a gradual increase in the serum creatinine level with time, with an associated time-related decrease in creatinine clearance. The relation between systemic hypertension and renal dysfunction is not yet clear.

To evaluate renal dysfunction further, 47 patients who underwent transplantation before December 1980 and were given azathioprine and prednisone for immunosuppression were compared with 32 recipients who received cyclosporine and prednisone.[11] An adverse effect on kidney function of long-term cyclosporine therapy is suggested by the divergent plot of the reciprocal of the serum creatinine level in the two populations (Fig. 8). Glomerular filtration rate in the azathioprine group was significantly ($p < 0.005$, unpaired two-tailed *t*-test) higher at all times after the first post-transplant month.

To define the renal injury associated with long-term cyclosporine therapy, detailed physiologic studies were performed in 17 consecutive 1-year survivors receiving.cyclosporine. For comparison, the same studies were performed in 13 unselected, long-term, azathioprine-treated control patients.[11] Inulin clearance was determined as a precise measure of glomerular filtration rate in the two groups. Fig. 9 demonstrates that inulin clearance in azathioprine controls was usually normal and always exceeded 70 mL/min. By contrast, inulin clearance in cyclosporine recipients was invariably below normal, sometimes severely so. There was almost no overlap between the two populations, with the average glomerular filtration rate in cyclosporine recipients reduced to only 51 mL/min versus 92 mL/min after 1 year of therapy.

To examine tubular function, the para-amino hippurate extraction ratio was measured by sampling renal venous blood during the catheterization of the right side of the heart. Although not significantly different from azathioprine controls, para-amino hippurate extraction was depressed to a subnormal value of 72% in patients receiving cyclosporine. The patients' ability to excrete a dilute urine was determined after giving 1.5 L of water orally during a 90-minute period. Both groups were able to lower urinary osmolarity below that in plasma. However, the free water clearance was appreciably reduced in cyclosporine-treated patients to 3 mL/min compared with 5.1 mL/min in azathioprine-treated patients. Thus, there was both proximal and distal tubular dysfunction in cyclosporine-treated patients.

To elucidate the cause of the reduced glomerular filtration rate associated with long-term cyclosporine therapy, several hemodynamic parameters were evaluated. Cardiac output was similar in the two groups, averaging just under 6 L/min. Cyclosporine-treated recipients differed, however, in that arterial hypertension was prevalent and renal blood flow, measured by the clearance and extraction of para-amino hippurate, was appreciably depressed to 501 mL/min compared with 836 mL/min. Dividing the renal pressure drop by blood flow showed that renal vascular resistance more than doubled in cyclosporine-treated patients.

To determine whether the cyclosporine-induced reduction in glomerular filtration rate was hemodynamically mediated or whether alterations in the glomerular cell wall were responsible, the fractional clearance of neutral dextrans of graded size was examined. It did not differ significantly between the two groups. However, for the first 24 to 34 angstrom intervals in patients receiving cyclosporine, the fractional clearance profile tended to be depressed below that in the azathioprine group. If one compares the predicted effects of a selective reduction in renal perfusion, where all determinants of glomerular filtration, except renal blood flow, have been held constant, then a selective fall in blood flow should uniformly enhance, and not depress, the fractional dextran clearance. Thus, the fall in renal blood flow from 836 to 501 mL/min in the cyclosporine group cannot wholly account for the dextran-clearance profile. Accordingly, the fractional clearances of dextran in each group were subjected to a theoretical analysis of solute transport through an isoporous membrane. From this, two membrane parameters were derived: first, the mean radius of functional pores perforating the glomerular capillary wall was determined to approximate 61 Å in each group, a value similar to that found previously in normal subjects; second, the ratio of total pore surface area to pore length may be equated with the total number of pores occupying the membrane to provide the pore "density". It was reduced from a normal value of 22 in azathioprine controls to only 15 in cyclosporine recipients. The disparity in pore density is comparable to the difference in glomerular filtration rate between the two groups, suggesting that the loss of surface area for filtration may be the mechanism by which long-term cyclosporine therapy lowers the glomerular filtration rate. To explore further the structural correlates of this finding, five cyclosporine-treated patients in whom the glomerular filtration rate was substantially reduced underwent renal

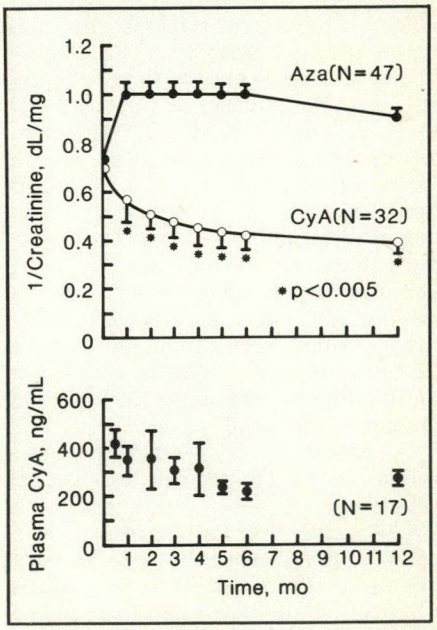


FIG. 8—Renal function in heart transplantation. Aza = azathioprine group, CyA = cyclosporine group.

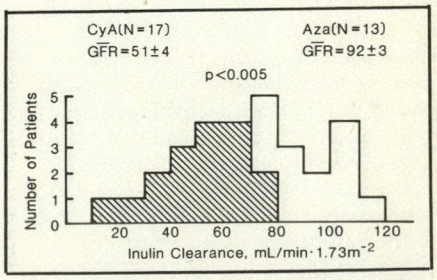


FIG. 9—Mean glomerular filtration ($\overline{GFR}$) rate at 1 year in cyclosporine-treated patients (CyA) was invariably below normal and nearly always less than that in unselected control patients treated on long-term basis with azathioprine (Aza).

biopsy. Light microscopy revealed tubular atrophy and a remarkable fibrosis in the interstitium. Electron microscopy showed that the basement membrane of tubular cells was thickened and there was a variable loss of the brush border. Convoluted tubule cells revealed diffuse loss of organelles and nuclear swelling alternating with nuclear pyknosis and loss of cytosol. Thus, growing evidence implicates cyclosporine as a tubular cell toxin. Although these findings are striking, the apparent deterioration in renal function over the first year after transplantation does not appear to be progressive over the subsequent 1 to 2 years. Therefore, we are guardedly optimistic about the stabilization of renal dysfunction in patients who received cyclosporine after heart transplantation. We have not yet discounted the prospect of using cyclosporine in the first 2 to 3 months after transplantation, and then switching to azathioprine, but further long-term data are required before we implement this strategy.

Measures that we believe useful to minimize postoperative renal dysfunction include: (a) use of less than 18 mg/kg of cyclosporine preoperatively and postoperatively in the presence of renal dysfunction; (b) daily monitoring of serum cyclosporine levels for at least 1 week postoperatively, aiming for levels of 150 to 250 ng/mL; (c) use of mannitol during cardiopulmonary bypass and then postoperatively with each dose of cyclosporine during the initial hospitalization; (d) maintenance of an optimal cardiac filling pressure; (e) use of renal effective doses of dopamine and (f) use of diuretics to maintain an hourly urine output of at least 1 mL/kg.

Myocardial fibrosis.—As in the kidney, a fine interstitial myocardial fibrosis starts within several weeks of treatment with cyclosporine.[12] At least 10 patients at 6 months, 18 at 1 year and 2 at 2 years have been assessed for evidence of myocardial restriction, both before and after volume loading with 0.9% saline. Although the long-term results of this fibrosis are not known, there is no evidence that it leads to myocardial damage of physiologic importance.

Headaches.—Although headaches are common early on in the course of cyclosporine therapy, they are generally thought to be due to a hyperdynamic circulation, hypertension and perhaps cerebral edema. In general, headaches can be controlled with antihypertensive therapy and analgesics. Usually within 1 to 3 weeks after transplantation, headaches are no longer a problem.

Hirsutism.—Hair growth may be striking with a general increase in body and scalp hair that becomes darker, thicker and wavier. This may be of concern to women, cosmetically.

Tremor.—A fine resting tremor is occasionally present for the first few weeks after transplantation, but it also resolves with time.

Hepatic dysfunction.—Transient elevation of liver enzymes and total bilirubin levels occur in most patients early after transplantation, but both usually return to baseline levels within 2 to 4 weeks after transplantation.

Interaction with rifampin.—Rifampin has been demonstrated to induce production of liver microsomal enzymes[13] and enhance the metabolic effect of prednisone.[14] In two patients with *Aspergillus fumigatus* pulmonary infection, in-vitro synergy studies demonstrated a potential benefit for them with amphotericin B combined with rifampin. In both patients, the requirements for cyclosporine increased three to fivefold within several days of beginning rifampin therapy.[15] In one patient, it was difficult to maintain satisfactory cyclosporine levels, and acute rejection occurred. Despite several treatment courses, the rejection never satisfactorily resolved and the patient ultimately died of acute and chronic rejection. In the second patient, the infection appeared to resolve and it was anticipated that renal dysfunction would ensue if the rifampin was discontinued without first lowering the cyclosporine dosage. Accordingly, the cyclosporine was returned to the original maintenance dosage at the same time that the rifampin was discontinued. Nevertheless, the serum creatinine level doubled and the creatinine clearance decreased to one half of its baseline value for several days before recovery. Others[14] have also reported a marked increase in cyclosporine requirements in renal transplant recipients who have required rifampin therapy.

Comparative Costs for Heart Transplantation

As of March 1983, the average cost per patient for cardiac transplantation in 48 patients treated with cyclosporine was nearly $30 000 less than in 97 patients given azathioprine. This difference was also reflected in the median cost of $63 000 as opposed to $91 000.

Cyclosporine in Heart-Lung Transplantation

Historically, the results of human heart-lung transplantation and lung transplantation have been disappointing. In three heart-lung transplantations done in 1968, 1969 and 1971, no patient survived beyond 23 days and each died from respiratory complications.[16-18] Similarly, of 39 patients who have undergone lung transplantation, only 2 have survived beyond 2 months (6 and 10 months).[19] Use of steroid immunosuppression contributed importantly to each patient's death of pneumonia or tracheobronchial disruption, by preventing anastomotic healing. With the successful introduction of cyclosporine in animal cardiac transplantation[20-22] and human renal transplantation,[23] the elimination or reduction of the requirements for steroids in solid-organ transplantation became a possibility. Experiments begun in 1979 using cyclosporine in primate heart-lung transplantation by Reitz and associates[24] at Stanford strongly supported a move towards clinical application of the procedure. Two primates are still alive and well at 4.5 and 5 years after transplantation. Stimulated by the primate experience and the success with cyclosporine in human heart transplantation, a program in human heart-lung transplantation was begun in March 1981.[25]

Recipient Selection

From March 1981 until May 1984, 19 heart-lung transplantations were performed in 13 men and 6 women ranging in age from 22 to 45 years (Table I). Twelve had congenital heart disease with secondary pulmonary hypertension, and 7 patients had primary pulmonary hypertension. Although a large group of patients with chronic obstructive pulmonary disease, pulmonary fibrosis or cystic fibrosis are conceivably suitable candidates, none in this group have yet undergone transplantation at Stanford University.

Operative Technique and Postoperative Management

The details of operative technique and postoperative management of heart-lung transplantations have been reported previously.[26] The operative technique has been modified in the last 13 patients so that: the lungs are cooled with modified Collins II solution; the heart and both lungs in the recipient are removed separately so that visualization of the bronchial arteries and of both the vagal and phrenic nerves is better; the back wall of the left pulmonary artery is left intact thereby minimizing the likelihood of injuring the recurrent laryngeal nerve and, during implantation, both lungs are bathed with cold (4°C) Physiosol (balanced salt) rather than Collins II (balanced salt, high in potassium) solution, to prevent undesirable potassium absorption and hyperkalemia. Modification of the operative technique, however, has not alleviated the problem of bleeding requiring re-exploration (nine patients). All patients received antibiotics (cefamandole, nafcillin and erythromycin) perioperatively.

Immunosuppression

The immunosuppressive regimen used in all patients consisted of cyclosporine, 14 to 18 mg/kg, orally 6 hours before transplantation, and then postoperatively in divided doses according to targeted serum levels between 100 and 300 ng/mL. Three doses of antithymocyte globulin of rabbit origin (2.5 mg/kg) were given intramuscularly to each patient, immediately following induction of anesthesia, then on postoperative days 1 and 2. The determining factor for the second postoperative dose of rabbit antithymocyte globulin was an absolute T-rosette level exceeding $100/mm^3$ the day after the first postoperative dose. Methylprednisolone sodium succinate, 500 mg intravenously, was given after cardiopulmonary bypass, then 125 mg intravenously every 8 hours for three doses. No further steroids were given in the subsequent 2 weeks, during which azathioprine, 1 to 2 mg/kg orally, was given daily if the leukocyte count was greater than $4 \times 10^9/L$. After 2 weeks, prednisone was begun at 0.2 to 0.3 mg/kg daily and the azathioprine was discontinued. Rejection episodes were diagnosed by endocardial biopsy.

Results

Of the 19 patients transplanted, as of March 1984, 13 survived the operation (operative mortality defined as death within 30 days of transplantation) (Table I) and were fully rehabilitated; 12 were still alive.

Of the six operative deaths, two patients died of multisystem organ failure, one of lung failure manifested, immediately following attempts to discontinue cardiopulmonary bypass, as a severe loss of alveolar-capillary integrity and massive pulmonary edema, two of pulmonary insufficiency on postoperative days 16 and 33 from undetermined causes (implantation response and rejection or infection, or both?) and one patient died of a myocardial infarction 15 months after transplantation.

Fourteen episodes of cardiac rejection have been diagnosed by cardiac biopsy, demonstrating a mononuclear cellular infiltrate with myocyte necrosis on histologic examination. Thirteen of the episodes occurred within 90 days of transplantation. Each episode was treated successfully with three 1-g/d pulses of methylprednisolone sodium succinate.

Until recently, we believed that both pulmonary and cardiac rejection were accurately reflected in all cases by endocardial biopsy. We also assumed that

Table I—Clinical Summary of the Heart-Lung Transplant Recipients

Patient no.	Age, yr	Sex	Diagnosis	Treated rejection episodes, postop. day	Form of rejection	Infection	Initial hospital discharge, d	Survival, d
1	45	F	PPH	11, 25, 45	Cardiac cellular infiltrate, MN	Herpes (cutaneous)	85	1146
2	30	M	E	235, 1041	Cardiac cellular infiltrate, MN (pulmonary infiltrate, pulmonary HPT, cardiac graft atherosclerosis)	CMV (systemic)	46	1090
3	29	F	E	X		X	4	4
4	40	M	E	86	Cardiac cellular infiltrate, MN	Recurrent lung infection (bronchiectasis)	46	961
5	37	F	PPH	21, 52	Cardiac cellular infiltrate, MN	—	64	881
6	29	F	PPH	X	X	X	23	23
7	22	M	E	X	X	X	0	0
8	40	M	E	—	—	*Bacteroides* (blood and lung), CMV (systemic)	40	542
9	22	M	E	15, 22, 211	Cardiac cellular infiltrate, MN, pulmonary infiltrate	*Enterococcus* (lung)	38	538
10	28	M	E	23, 29, 56, 443	Cardiac cellular infiltrate, MN, cardiac graft atherosclerosis, myocardial infarction	—	39	443
11	38	M	E	—	—	—	38	476
12	32	M	E	—	—	CMV (systemic), *Klebsiella* (pulmonary), recurrent lung infection (bronchiectasis)	46	347
13	33	M	E	14	Cardiac cellular infiltrate, MN	*Serratia* (pulmonary), CMV (systemic)	51	344
14	28	F	PPH	X	X	*Candida* (pulmonary)	16	16
15	42	M	E	X	X	*Legionella* (pulmonary), *Serratia, Enterococcus* (pulmonary)	33	33
16	22	M	PPH	29	Cardiac cellular infiltrate, MN	*Serratia, Hafnia alvei* (pulmonary)	49	177
17	37	M	PPH	—	—	*Enterobacter, Serratia, Staphylococcus* (pulmonary)	63	150
18	33	F	PPH	In hospital				
19	40	M	E	In hospital				

PPH = primary pulmonary hypertension, E = Eisenmenger's syndrome, MN = myocyte necrosis, HPT = hypertension, CMV = cytomegalovirus, X = not applicable.

pathologic lung rejection would invariably demonstrate a classic cellular pattern. Although in general these two assumptions hold true, it appears that, with cyclosporine immunosuppression, neither is entirely accurate. Primate heart-lung transplantation studies have demonstrated that severe cellular lung rejection may occur without appreciable heart rejection.[27] Furthermore, two patients (cases 2 and 9) suffered late pulmonary infiltration on lung biopsy but no cardiac rejection. Over the previous 4 months, both had had serum cyclosporine levels below 150 ng/mL and in patient no. 9 a restrictive pattern that had developed along with the infiltration partially resolved with a return towards normal lung volumes, compliance and roentgenographic appearance following steroid therapy; in patient no. 2, severe coronary atherosclerosis and pulmonary hypertension were documented shortly after the development of the lung infiltration. A third patient who had cyclosporine levels below 150 ng/mL for 7 months died suddenly and was found to have an extensive myocardial infarction and graft atherosclerosis. The occurrence of pulmonary hypertension and graft atherosclerosis and perhaps even the late pulmonary infiltration may represent a less-common form of vascular rejection, perhaps humorally mediated. That the pulmonary changes and graft atherosclerosis occurred only in these three patients following a 4- to 6-month period with low cyclosporine levels (less than 150 ng/mL) suggests, but does not prove, cause and effect. Nevertheless, stimulated by these findings, our current recommendation is to aim for serum trough cyclosporine levels of 200 to 300 ng/mL, rather than our previous range of 100 to 300 ng/mL.

A similar degree of renal dysfunction (elevated creatinine and blood urea nitrogen levels) and hypertension requiring therapy occurred in heart-lung recipients as in the heart recipients.

Perhaps the most unusual complication following heart-lung transplantation was the development of the "implantation" response in the lungs of 9 of the 13 long-term survivors. This reponse, which has been described previously,[28] is characterized by perihilar infiltration that may become confluent and must be distinguished from infection and rejection. These changes generally occur and resolve between 7 and 28 days after transplantation, and are associated with hypoxemia and decreased lung compliance. Factors exclusive of rejection and infection that have been considered possible in the pathogenesis include lymphatic, bronchial arterial or neural interruption, or both, mechanical trauma from handling of lungs, and the perfusate used to cool the lungs. The etiology of this pulmonary response, however, is unclear since no patients or primates have yet had a diagnostic lung biopsy. In fact, rejection or immune complex disease could still be a factor since all patients appear to improve when azathioprine is discontinued and use of prednisone is started on postoperative day 14; one patient has been documented as having elevated levels of circulating immune complexes and decreased serum complement (unpublished data).

Infection during the initial hospitalization has been of grave concern, particularly in recipients who had an implantation response. Table I documents only a modest number of non-fatal infectious episodes. Scrupulous donor selection, vigorous investigation and surveillance for infection, use of antibiotics prophylactically and in many instances, prolonged use of broad-spectrum antibiotics during the implantation response likely contributed to the relatively low frequency of infectious episodes. Localized bronchiectasis with recurrent episodes of pneumonia have developed in two long-term survivors but no malignant process has been found.

Summary

In summary, 13 of 19 patients are alive 1 to 38 months after heart-lung transplantation. Notwithstanding the important efforts by the many investigators involved with the heart-lung transplantation program, none of this would be possible were it not for the unique immunosuppressive properties of cyclosporine.

Experience with the use of cyclosporine in both heart and heart-lung transplantation indicates that when used in combination with low doses of prednisone, important improvement in allograft survival can be achieved. That both early and late rejection (cellular and humoral) and infection still occur in both groups of patients, along with hypertension and renal dysfunction secondary to cyclosporine use, demands that we continue our efforts to control the immune system and eliminate unwanted drug side effects.

Addendum

As of January 1985, 352 heart allografts had been placed in 325 recipients, and 24 patients had received 25 heart-lung transplants. Conclusions based on data generated as of January and March 1984 for the two groups respectively, with regard to survival and complications, still applied and they support the continued use of cyclosporine, with the guidelines suggested to minimize toxicity. In some patients with declining renal function, azathioprine may have to replace cyclosporine for immunosuppression.

References

1. OYER PE, STINSON EB, JAMIESON SW, HUNT S, REITZ BA, BIEBER CP, SCHROEDER JS, BILLINGHAM M, SHUMWAY NE: One year experience with cyclosporin A in clinical heart transplantation. *Heart Transplant* 1982; 1: 285-90

NOW TREAT POST-OPERATIVE PAIN BEFORE YOU LEAVE THE O.R.

MARCAINE* NERVE BLOCK OR INFILTRATION BEFORE CLOSURE GIVES UP TO 15 HOURS OF POST-OPERATIVE PAIN RELIEF.[1]

POST-OPERATIVE STRESS can be substantially reduced by preventing post-operative pain in those critical first hours after surgery.[2]

Marcaine blocks this pain, giving an easier, quicker recovery; often without the need for narcotic analgesics.[3]

MARCAINE

FOR PAIN RELIEF THAT STARTS IN THE O.R.

Winthrop

Winthrop Laboratories
Division of Sterling Drug Ltd.**
Aurora, Ontario L4G 3H6
*Reg. Trade Mark
**Registered User

PAAB
CCPP

References
1. Ocker, Glenn A.: Bupivacaine: A New Longer Lasting Local Anesthetic. Journal of the American Podiatry Association. Vol. 66, No. 8, Aug. 1976, pp. 618-630.
2. Scott, D.B.: Postoperative Pain Relief. American Society of Regional Anesthesia. Suppl. 1982: 7:S110-S113.
3. Rochowanski, E., Kreiser, R.D., and Morris, L.E.: Caudal Anaesthesia with Bupivacaine (Marcaine) for Anal Surgery: A Clinical Trial. Canadian Anaesthetist's Society Journal 1971: 18:18-22.

2. JAMIESON SW, BALDWIN J, STINSON EB, et al: Clinical heart-lung transplantation. *Transplantation* 1984; 37: 81–4
3. BAUMGARTNER WA, REITZ BA, OYER PE, STINSON EB, SHUMWAY NE: Cardiac homotransplantation. *Curr Probl Surg* 1979; 16: 1–61
4. OYER PE, STINSON EB, REITZ BA, RANEY AA, BAUMGARTNER WA, SHUMWAY NE: Diagnosis and treatment of acute cardiac allograft rejection. *Transplant Proc* 1979; 11: 296–303
5. DAWKINS KD, OLDERSHAW PJ, BILLINGHAM ME, HUNT SA, OYER PE, JAMIESON SW, POPP RI, STINSON EB, SHUMWAY NE: Changes in diastolic function as a non-invasive marker of cardiac allograft rejection. *Heart Transplant* 1984; 3: 286–94
6. BIEBER CP, HUNT SA, SCHWINN A, JAMIESON SW, REITZ BA, OYER PE, SHUMWAY NE, STINSON EB: Complications in longterm survivors of cardiac transplantation. *Transplant Proc* 1981; 13: 207–11
7. STINSON EB, Competitive Grant Renewal, National Heart, Blood, and Lung Institute: *Clinical Heart and Heart Lung Transplantation,* Feb. 1982
8. HANTO DW, SAKAMOTO K, PURTILO DT, SIMMONS RL, NAJARIAN JS: The Epstein–Barr virus in the pathogenesis of posttransplant lymphoproliferative disorders. Clinical, pathologic, and virologic correlation. *Surgery* 1981; 90: 204–13
9. PENN I: Problems of cancer in organ transplantation. *Heart Transplant* 1982; 2: 71–7
10. GRIFFITH BP, HARDESTY RL, THOMSON ME, DUMMER JS, BAHNSON HT: Cardiac transplantation with cyclosporine: the Pittsburgh experience. *Heart Transplant* 1983; 2: 251–6
11. MORAN M, NEWTON L, PERLROTH M, MYERS B: Cyclosporine nephrotoxicity in man (abstr). *Proc Am Soc Nephrol* 1983; 16: 209
12. BILLINGHAM ME: Diagnosis of cardiac rejection by endomyocardial biopsy. *Heart Transplant* 1981; 1: 25–9
13. MCALLISTER WA, THOMPSON PJ, AL-HABET SM, ROGERS HJ: Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J* [*Clin Res*] 1983; 286: 923–5
14. LANGHOFF E, MADSEN S: Rapid metabolism of cyclosporin and prednisone in kidney transplant patient receiving tuberculostatic treatment (C). *Lancet* 1983; 2: 1031
15. MODRY DL, STINSON EB, OYER PE, JAMIESON SW, BALDWIN J, SHUMWAY NE: Acute rejection and massive cyclosporine requirements in heart transplant recipients treated with rifampin. *Transplantation* (in press)
16. COOLEY DA, BLOODWELLRD, HALLMAN GL, NORA JJ, HARRISON GM, LEACHMAN RD: Organ transplantation for advanced cardiopulmonary disease. *Ann Thorac Surg* 1969; 8: 30–46
17. LILLEHEI CW: In discussion of WILDEVUUR CR, BENFIELD JR: A review of 23 human lung transplantations by 20 surgeons. *Ann Thorac Surg* 1970; 9: 489–515
18. BARNARD CN, COOPER DK: Clinical transplantation of the heart: a review of 13 years' personal experience. *J R Soc Med* 1981; 74: 670–4
19. VEITH FJ, MONTEFUSCO C, KAMHOLZ SL, MOLLENKOPF FR: Lung transplantation. *Heart Transplant* 1983; 2: 155–64
20. CALNE RY, WHITE DJG, ROLLES K, SMITH DP, HERBERTSON BM: Prolonged survival of pig orthotopic heart grafts treated with cyclosporin A. *Lancet* 1978; 1: 1183–5
21. JAMIESON SW, BURTON NA, BIEBER CP, REITZ BA, OYER PE, STINSON EB, SHUMWAY NE: Cardiac-allograft survival in primates treated with cyclosporin A (C). *Lancet* 1979; 1: 545
22. KAWAHARA K, SUTHERLAND DE, RYNASIEWICZ JJ, NAJARIAN JS: Prolongation of heterotopic cardiac allografts in rats by cyclosporin A. *Surgery* 1980; 88: 594–600
23. CALNE RY, ROLLES K, WHITE DJ, et al: Cyclosporin-A in clinical organ grafting. *Transplant Proc* 1981; 13 (1 pt 1): 349–58
24. REITZ BA, BURTON NA, JAMIESON SW, BIEBER CP, PENNOCK JL, STINSON EB, SHUMWAY NE: Heart and lung transplantation: autotransplantation and allotransplantation in primates with extended survival. *J Thorac Cardiovasc Surg* 1980; 80: 360–72
25. REITZ BA: Heart and lung transplantation. *Heart Transplant* 1981; 1: 80–1
26. JAMIESON SW, BALDWIN J, REITZ BA, et al: Combined heart and lung transplantation. *Lancet* 1983; 1: 1130–2
27. SCOTT WC, HAVERICH A, BILLINGHAM ME, DAWKINS KD, JAMIESON SW: Lethal lung rejection without significant cardiac rejection in primate heart-lung allotransplants. *Heart Transplant* 1984; 4: 33–9
28. SIEGELMAN SS, SINHA SBP, VEITH FJ: Pulmonary reimplantation response. *Ann Surg* 1973; 177: 30–6

WILBERT J. KEON, MD, FRCSC; SUSAN C. MENZIES, RN, MHA; COLIN M. LAY, PH D

Cost of Coronary Artery Bypass Surgery: a Pilot Study

The increasing concern about the high cost of health care led the authors to conduct a pilot study on the overall cost and cost variability for patients who underwent coronary artery bypass grafting. They reviewed the charts of 50 randomly selected patients to determine actual costs of catheterization and bypass grafting. Four patients had single-vessel disease, 12 double- and 34 triple-vessel disease and 13 had moderate to severe impairment of ventricular function. The length of hospital stay ranged from 8 to 43 days (mean 16.5 days). The duration of stay in the recovery room and intensive care unit ranged from 21 to 356 hours (mean 91.6 hours). Operative time ranged from 2 to 6.5 hours (mean 3.95 hours). Using several accepted cost-allocation methods, the authors developed a valid, complete breakdown of clinical and nonclinical costs. Total cost was directly related to the length of hospital stay, left ventricular function, secondary diagnosis and number of diseased vessels. Further studies will address clinical factors related to cost and cost effectiveness of coronary artery bypass grafting as opposed to other forms of treatment for coronary artery disease.

Les coûts élevés des soins de santé font l'objet d'un souci croissant. Les auteurs ont donc mené une étude pilote des coûts globaux et de leur variation chez des patients soumis à un pontage aorto-coronarien. Ils ont étudié les dossiers de 50 patients choisis au hasard afin d'établir les coûts d'un cathétérisme et d'un pontage. L'oblitération coronarienne était simple chez 4 patients, double chez 12 et triple chez 34; 13 malades présentaient une insuffisance ventriculaire moyenne à sévère. La durée d'hospitalisation a varié de 8 à 43 jours (16.5 jours en moyenne). Le séjour en salle de réveil et aux soins intensifs a duré de 21 à 356 heures (moyenne de 91.6 heures). L'opération a duré de 2 à 6.5 heures (moyenne de 3.95 heures). A l'aide de plusieurs méthodes de facturation reconnue, les auteurs ont établi une répartition complète et acceptable des coûts cliniques et non cliniques. Le coût total était directement relié à la durée du séjour à l'hôpital, à l'état de la fonction ventriculaire gauche, aux diagnostics secondaires et au nombre de pontages requis. Des études subséquentes s'intéresseront aux facteurs cliniques reliés aux coûts et au rapport coûts/bénéfices du pontage aorto-coronarien par rapport à d'autres formes de traitement de la maladie coronarienne.

The high cost of health care is causing increasing concern to the public, government and health-care professionals. Coronary artery disease, particularly its surgical treatment, places an enormous burden on all. The University of Ottawa Heart Institute, in conjunction with the Health Administration Program of the Faculty of Administration, University of Ottawa, has embarked on studies to determine the cost and cost effectiveness of coronary artery bypass grafting. The first step has been a pilot study to determine the overall cost and cost variability for patients who undergo bypass grafting. The question of the cost of heart surgery is of interest in Canada because we lack the basic data for public decision-making about funding for increases or changes, or both, in this area. The lack of data is common to the health-care system in all provinces and has specific impact on cardiovascular disease, Canada's number one health-care problem. It is well recognized how widely costs vary among health-care institutions, even among those providing a similar type or range of services. While such institutions may face identical market prices for their goods and services, the degree of efficiency in the use of resources will ultimately determine the net cost of care. Identifying and measuring the many interrelated input factors and tracing the connection between them and specific medical services require a tailored approach in each health-care facility. To complicate cost analysis further, and this is especially true of hospitals, management systems are not designed to provide the requisite information. Accounting procedures typically aggregate costs, so that it is difficult to determine the relation between resource consumption and production of those resources. Cost analysis must often start at the bottom and work up, adapting the methodology to the obstacles of incomplete, invalid or inaccurate primary data.

Methodology

The University of Ottawa Heart Institute at the Ottawa Civic Hospital is a free-standing structure devoted to the prevention, investigation, treatment — both medical and surgical — and the rehabilitation of patients with cardiovascular disease. It has 125 set-up beds, including 8 surgical and 8 medical intensive-care beds with an additional 6 recovery room beds, 8 day-care and 4 emergency resuscitation beds. We perform more than 1000 operative procedures annually of which 750 are bypass grafting.

Cost for the services provided for patients who undergo coronary artery bypass grafting were determined according to accepted disease-costing methodology.[1] The first step was to design a cost-centre matrix that integrated six arbitrary stages of the patient's hospital stay into admission, preoperative, ward, operating room, recovery room and surgical intensive care, and postoperative ward and discharge. With the hospital cost centres defined in previous research at the Ottawa Civic Hospital,[2] these cost centres were divided into three categories: support departments, diagnostic and therapeutic departments and patient-care departments. All hospital operating costs and treatment elements applicable to the procedure were identified and classified

From the University of Ottawa Heart Institute and Faculty of Administration, Program in Health Administration, University of Ottawa, Ottawa, Ont.

Accepted for publication Oct. 22, 1984

Reprint requests to: Dr. Wilbert J. Keon, Director General, University of Ottawa Heart Institute, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ont. K1Y 4E9

as direct, indirect or overhead. Costs were assigned to an individual patient and aggregated to obtain the cost of an episode of illness for coronary artery bypass grafting (Fig. 1).[3] The cost of labour on the wards before and after operation was determined using a work-sampling ratio delay study over a 7-day period.[4,5] The hospital charts of 50 randomly selected patients who underwent coronary artery bypass were reviewed in detail to determine the actual cost of admission for catheterization or separate admission for operation, or both. Professional fees were determined by recording the actual amounts reimbursed by the provincial government plans to the medical staff involved in the treatment: surgeons, anesthetists, surgical assistants, cardiologists and radiologists.

Clinical Profile of Patients

We reviewed the charts of 50 patients (42 men, 8 women) who underwent coronary artery bypass grafting between April and September 1983, excluding patients who underwent reoperation or who died in hospital. The mean age of the patients was 55.3 years (ranging from 39 to 73 years). This is representative of the male to female ratio and age range of our total patient population. Four patients had single-vessel, 12 double-vessel and 34 triple-vessel disease. Seven had been operated upon urgently and 43 electively. Thirteen had poor ventricular function (class III or IV[6]) and the remaining 37 had normal function or mild impairment. Seven patients underwent additional procedures: coronary endarterectomy in six and left ventricular aneurysm resection in one; two patients required intra-aortic balloon pump assistance early postoperatively. The total length of hospital stay including the stay for cardiac catheterization averaged 16.5 days (ranging from 8 to 43 days).

Total Episode Cost

An episode of illness for this costing study is defined as a stay in hospital for the surgical procedure and separate admission for cardiac catheterization. Twenty-five patients underwent catheterization during the admission for operation, three had catheterization as outpatients and one at a different hospital (that single procedure was not costed). The episode costs are the total costs for all treatment elements during the hospital stay. The total costs varied from $6387. to $18 415. (Canadian 1983 dollars) with an average cost of $9595. This total comprises two parts: professional fees and hospital costs.

The hospital costs were broken down into five categories: cardiac catheterization; laboratory, radiologic and pharmaceutical expenses; surgical ward (including preoperative coronary care unit); operative procedure; recovery room and surgical intensive care unit. The minimum, maximum and mean costs in each of these subcategories are summarized in Table I.

The total episode cost, not surprisingly, was directly related to length of hospital stay (Table II). It was also directly related to the number of diseased vessels, secondary diagnoses, left ventricular dysfunction and age (Table III). It was not related to sex, emergency category of a patient, number of bypass grafts placed or auxiliary procedures performed.

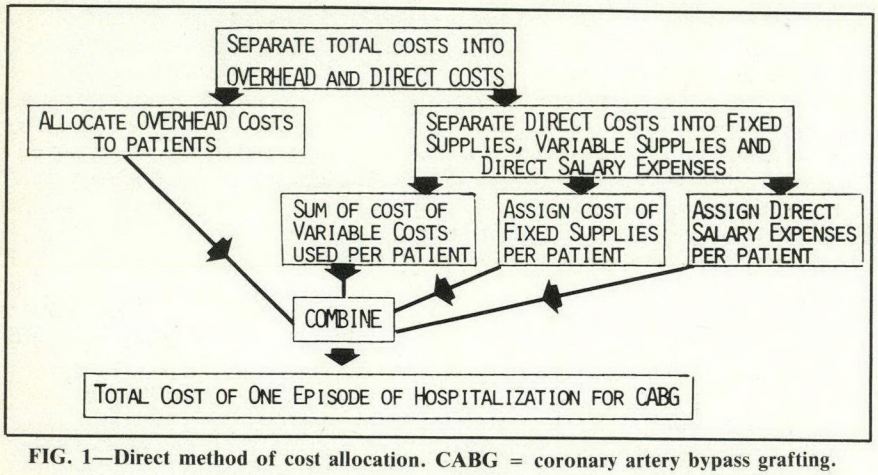


FIG. 1—Direct method of cost allocation. CABG = coronary artery bypass grafting.

Table I—Hospital Costs

Category	Minimum, $	Maximum, $	Mean, $
Catheterization	—	—	409*
Laboratory, radiology, pharmacy	349	1 621	555
Surgical ward including coronary care unit	1 205	11 828	2 750
Coronary care unit alone, preop	474	9 006	1 828
Operation and recovery room —surgical intensive care unit	2 332	8 894	3 629
Operation alone	1 700	1 943	1 817

*One charge only.

Table II—Episode Cost Versus Length of Hospital Stay

Length of stay, d	No.	Range, $	Mean, $
9	5	6 389– 8 143	7 584
10–12	15	6 949–16 183	9 319
14–16	6	8 458–10 363	9 702
17–19	7	7 568–10 804	9 126
20–29	10	8 931–18 415	13 067
30–43	3	10 872–14 997	13 159

Discussion

Establishing a firm estimate for the surgical cost of treatment for coronary artery disease is the first step in analysing cost effectiveness. We carried out a detailed study of the cost of treating 50 patients who underwent coronary artery bypass grafting. Fig. 2 shows the distribution of total costs ranging from the lowest to the highest for each patient. For the first time we know the actual costs of treating a group of patients who had heart surgery in Canada. We studied the treatment process for patients who underwent coronary artery bypass grafting, carrying out a detailed cost analysis in every department of the hospital participating in their treatment. We studied their cost patterns and developed unit costs for every identifiable component of patient care as it appeared on the patient's medical chart and others such as administrative, overhead and capital equipment costs that were not recorded on the charts. We covered all direct and indirect aspects of care. These costs were then used together with a detailed chart review to develop an accounting for each patient.

In two other detailed costing studies done in the United States, the method of costing and reimbursement for patients' services was different from our own.[7,8] However, a broad comparison is possible after adding an annual inflationary

factor (10%) and converting American to 1983 Canadian dollars (25%). Although the institutions and the methodology were different, professional fees remain at a fairly constant percentage of the total hospital cost (Table IV), with professional fees representing 20% to 30% and hospital charges 70% to 80% of total costs. Stoney and colleagues,[8] reporting from Vanderbilt University School of Medicine in Nashville, showed a considerable difference in hospital costs when they were subdivided. Most notably, nursing costs on the ward were half our costs, operating room expenses twice, catheterization procedures three times and blood 16 times our costs. It must be noted, however, that the cost of $21 per patient for blood in our institute refers only to the charges for cross-matching since the blood itself is free of charge. In a more recent American study, Jang and colleagues[9] compared the cost of surgery for single-vessel disease as opposed to percutaneous transluminal coronary angioplasty and quoted a cost for coronary artery bypass grafting of $15 580 in 1983 US dollars. There are no published Canadian costing studies in this area.

This pilot study is our first step towards dealing with disease costing and analysis of cost effectiveness at the University of Ottawa Heart Institute. We expect to refine further the costing components of care and to develop a patient care information system that will generate data for medical peer review. This will be of use in discussions of both the medical and economic aspects and will eventually lead to a study of the cost effectiveness of alternative forms of treatment for coronary artery disease.

Hospital information systems in Canada are in their infancy in the area of clinical patient information systems. With the development of cost data, not only will physicians and surgeons be able to present their cases from the clinical point of view, but they will also have the precise cost data with which to judge the economic implications of their decisions to use one form of investigation and treatment as opposed to another. An example of the potential for such knowledge is the development of a system for estimating the day of discharge, focusing on expeditious treatment and discharge of patients and thus reducing unnecessarily lengthy stays to which cost is directly related. This frees up beds to allow flexibility in the flow of patients. Other alternatives to investigate are the performance of cardiac catheterizations on an outpatient basis and the provision of less-expensive hostel-type inpatient care for patients from out of town or for those with minor complications who do not require the resources of the normal inpatient facilities.

One area of continuing concern is whether particular courses of treatment have long-term cost benefits for the individual patient and for society as a whole. So far, we have simply addressed ourselves to the cost of one mode of treatment. However, the proposed research will encompass the broader questions. The objective is to continue to treat patients as effectively, but also as economically, as possible. The added bonus of a clinical information system would be for administrative use in planning patient load and workloads in each department and institution as well as in budgeting and forecasting.

The days of open-ended financial attitudes on planning health care have passed. Improvements must come from within the system and be initiated by the physicians and surgeons concerned and must not be imposed by the funding bodies. Accurate and responsible disease costing studies are a prerequisite to this intelligent planning.

We thank Jann Darlington, David Kay, John MacIntyre, Janie Reed and Melissa Sonberg, master's degree students in the Health Administration Program, and Mrs. Katrin Smith, Research Assistant, University of Ottawa Heart Institute, for their assistance in this study.

Table III—Variables Affecting Episode Cost

Variable	No.	Range of cost, $	Mean cost, $
Age, yr			
37–49	15	6 387–16 183	8 616
50–59	17	7 329–16 224	9 603
60–73	18	7 317–18 415	10 404
No. of diseased vessels			
1	4	6 387– 8 143	7 624
2	12	7 329–18 415	9 319
3	34	6 949–16 224	9 702
Left ventricular function			
Poor	13	7 341–14 998	10 196
Good	37	6 387–18 415	9 383
Secondary diagnoses			
Diabetes	6	6 387–13 174	11 059
Hypertension	5	7 979–14 999	10 599
Peripheral vascular disease	5	7 317– 8 885	7 905
Transient ischemic attacks	2	8 303– 9 154	8 728
Chronic obstructive pulmonary disease	2	16 225–18 415	17 320
Total secondary diagnosis	20	6 387–18 415	10 549
Coronary artery disease alone	30	6 949–16 412	8 495

Table IV—Comparison of Hospital Costs (1983 Canadian Dollars)

Cost	Nashville,[8] $	Birmingham,[7] $	Ottawa, $	Loma Linda,*[9] $
Ward	1 268	–	2 749	–
Intensive care unit/d	684	–	474	–
Electrocardiogram	254	–	46	–
Operating room	3 729	–	1 800	3 600
Catheterization	1 151	–	408	–
Blood	324	–	21	–
Radiology	160	–	117	–
Pharmacy	–	800 (4.4%)	144 (1.5%)	–
Professional fees	6 344 (30%)	3 860 (20.6%)	2 254 (23.5%)	6 130 (31%)
Total in hospital	14 983 (70%)	14 104 (75%)	7 345 (76.5%)	13 350 (69%)
Total/episode	21 332	18 764	9 595	19 480

*Combined national study.

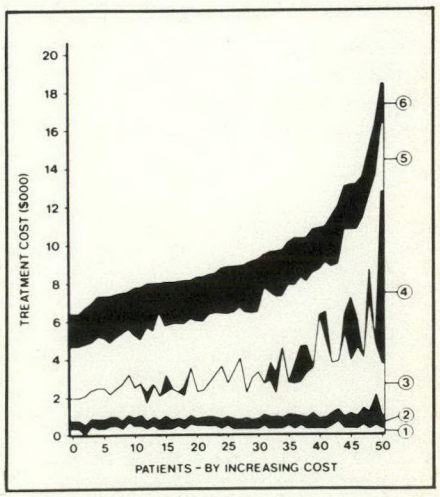


FIG. 2—Variability of costs of coronary artery bypass grafting for each of 50 patients. 1 = cost of coronary angiography (+ separate stay), 2 = laboratory, radiologic and pharmaceutical costs, 3 = surgical ward nursing, 4 = cost in coronary care unit preoperatively, 5 = recovery room and surgical intensive care unit costs, 6 = professional fees.

References

1. BABSON JL, HEIDEMANN EG, LAY CM: *Disease Costing Applied to Measuring the Cost of Treating Patients Undergoing Surgical Removal of the Gallbladder (Cholecystectomy)*, Master of Health Administration thesis, University of Ottawa, 1975
2. LAY CM, LOWRY E: Programme expense reporting project [internal report], Ottawa Civic Hospital, 1982
3. WILLIAMS SV, FINKLER SA, MURPHY CM, EISENBERG JM: Improved cost allocation in case-mix accounting. *Med Care* 1982; 20: 450–9
4. BARNES RM: *Motion and Time Study*, 5th ed, Wiley, New York, 1963: 517–54
5. ROCHE JF: Work sampling of nursing activities. In SMALLEY HE, FREEMAN JR (eds): *Hospital Industrial Engineering*, Reinhold, New York, 1966: 241–5
6. KEON WJ: Expectations of myocardial revascularization. *Can Med Assoc J* 1978; 118: 408–12
7. KRONENFELD JJ, CHARLES ED JR, WAYNE JB, OBERMAN A, KOUCHOUKOS NT, ROGERS WJ, MANTLE JA, RACKLEY CE, RUSSELL RO JR: Unstable angina pectoris: an examination of modes and costs of therapy. *Circulation* 1979; 60(2 pt 2): I16–I22
8. STONEY WS, ALFORD WC JR, BURRUS GR, FRIST RA, THOMAS CS JR: The cost of coronary bypass procedures. *JAMA* 1978; 240: 2278–80
9. JANG GC, BLOCK PC, COWLEY MJ, et al: Relative cost of coronary angioplasty and bypass surgery in a one-vessel disease model. *Am J Cardiol* 1984; 53: 52C–55C

WILLIAM J. WALL, MD, FRCSC;* JOHN H. DUFF, MD, FRCSC;*
CAMERON N. GHENT, MD, FRCPC;† CALVIN R. STILLER, MD, FRCPC;†
PAUL A. KEOWN, MD, FRCPC;† JUDITH L. KUTT, MD, FRCPC‡

Liver Transplantation: the Initial Experience of a Canadian Centre

At the University Hospital in London, Ont., 19 patients have received 24 liver transplants. The commonest indications for transplantation were primary biliary cirrhosis and cirrhosis from chronic active hepatitis. The first three patients in the series died of infectious complications. Eleven of the subsequent 16 recipients are alive from 5 months to 2½ years after transplantation. Eight patients who are alive more than 1 year after the operation have an excellent quality of life. Cyclosporine and steroids in combination are used for immunosuppression.

With current surgical techniques, modern immunosuppression and good patient selection, the restoration of patients with advanced irreversible liver disease to good health by liver transplantation is a realistic goal. Much effort and considerable resources are required to run a liver transplant program.

À l'Hospitalier Universitaire de London, Ont., 24 transplantations de foie ont été exécutées dans 19 bénéficiaires. Les indications les plus communes pour la transplantation étaient le cirrhose biliaire primaire et le cirrhose résultant de l'hépatite active chronique. Les trois premiers patients de la série moururent de complications infectieuses. Onze des 16 destinataires ultérieurs sont actuellement vivants après des périodes d'entre 5 mois et 2½ ans après la transplantation. Huit patients sont vivants après plus d'un an, et la qualité de leur vie est excellente. L'immunosuppression employée actuellement est une combinaison de cyclosporine et de stéroïdes.

À cause des techniques actuelles de chirurgie, et de l'immunosuppression moderne, ainsi que d'une sélection particulièrement efficace de patients, le rétablissement à la bonne santé des patients souffrant de maladies de foie irréversibles par la transplantation de foie est un but réaliste. L'effort et les ressources nécessaires à mettre sur pied un programme de transplantation sont en effet importants.

Almost 1000 human liver transplants have been performed since Starzl's first report more than 20 years ago.[1] The early procedures were plagued by technical complications, uncontrollable bleeding, infection and poor organ preservation, all of which resulted in high operative mortality and morbidity. Recently, however, results have improved substantially and 1-year survival rates following liver transplantation now approximate 70% in experienced hands.[2] The main reasons for the improved results have been better immunosuppression and more critical selection of recipients.

In the late 1970s we became convinced that some individuals with certain types of liver disease could benefit from liver transplantation. We believed that there was a need for this service in our area and that the results justified starting a program. This was an expansion of an already established program in renal transplantation at University Hospital in London, Ont., that now includes transplantations of heart, heart-lung and pancreas.[3,4] This report details our experience to date in transplantation of the liver.

Patients

Twenty-four orthotopic liver transplants have been performed in 19 patients (13 females, 6 males) (Table I). Three patients received two transplants and one patient received three. The recipients ranged in age from 14 to 58 years. The majority had primary biliary cirrhosis or cirrhosis from chronic active hepatitis (surface antigen negative) (Tables II and III). Recipients with a chronic liver condition had advanced disease with uncontrolled ascites, hypoalbuminemia, malnutrition, increasing jaundice, coagulopathy and encephalopathy in spite of ideal medical therapy. Two patients had previously undergone portacaval shunting for bleeding esophageal varices. Sixteen of the 19 recipients were hospitalized while awaiting transplantation because they were too sick to be managed at home. Transplantation was not recommended to patients with chronic liver disease until it seemed that life expectancy was measured in months or less. Three patients had acute liver failure from extensive liver necrosis and were trans-

Table I—Liver Transplants

Year	No. of recipients	No. of survivors
1977	1	0
1978	1	0
1981	1	0
1982	1	1
1983	4	3
1984	11	7
Totals	19	11

*From the *Department of Surgery, †Department of Medicine and ‡Department of Anesthesia, University Hospital, University of Western Ontario, London, Ont.*

Supported in part by grant M230A1 from the Medical Research Council of Canada and the Richard and Jean Ivey Fund

Presented at the annual meeting of the Canadian Transplantation Society, Montreal, PQ, Sept. 13, 1984, held in conjunction with the 53rd annual meeting of the Royal College of Physicians and Surgeons of Canada

Accepted for publication Jan. 29, 1985

Reprint requests to: Dr. William J. Wall, Department of Surgery, University Hospital, PO Box 5339, Station A, London, Ont. N6A 5A5

planted when they were in grade 4 liver coma, were ventilator-dependent, and had associated renal failure. The patients with acute liver failure were deemed to be dying and would not survive without a transplant. Important considerations in selecting patients were a stable psychosocial background and the absence of cardiopulmonary disease. Only one patient with malignant disease received a transplant. She had a multifocal, fibrolamellar hepatoma that was shown grossly to be confined to the liver.

Donor Operation

Livers were removed from donors in whom brain death had occurred as a result of head trauma or spontaneous intracranial hemorrhage. In 17 cases the donors were in hospitals outside London and the transplant team travelled to the donor hospital to remove the liver. The round-trip distances travelled by the donor team ranged from 290 to 3520 km. Livers were preserved in ice-cold Collins solution, using the in-situ flush technique and hypothermic storage.[5] The preservation times of the donor livers ranged from 1 h 51 min to 5 h 21 min (average 3 h 54 min). With one exception the kidneys were also removed from each liver donor for transplantation and in five of the donors the heart was also used for transplantation. The liver donors were blood-group compatible with the recipients but no other tissue matching was attempted.

Recipient Operation

The diseased recipient liver was removed and the donor organ placed in the orthotopic position. No pumping or venous bypass was used. The vascular anastomoses were performed in the following sequence: suprahepatic vena cava, portal vein, infrahepatic vena cava and hepatic artery. The bile duct was anastomosed end-to-end without a stent in all cases but one. One patient (no. 6) had a duct-to-Roux loop as a primary procedure. A fine polyethylene catheter was left in the common duct or gallbladder, or both, for postoperative cholangiography. The recipient anesthesia time ranged from 5 h 55 min to 10 h 55 min (average 7 h 24 min).

Immunosuppression

The first two patients in the series received Imuran and steroids for immunosuppression. All subsequent recipients received cyclosporine and steroids. Cyclosporine was given intravenously (2 to 3 mg/kg daily) after operation until the recipients could take it by mouth (10 to 15 mg/kg daily) in two divided doses, usually at the end of the first week after operation. Cyclosporine doses were aimed at maintaining serum trough levels of 150 to 200 ng/mL in the immediate postoperative period. Several months after transplantation, maintenance levels of 80 to 150 ng/mL were accepted. Serum levels were monitored by radioimmunoassay. Recently, concurrent high-pressure liquid chromatography (HPLC) assay has been used as a better indicator of parent compound only.[6] Methylprednisolone, 500 mg, was given intraoperatively after revascularization of the liver. Postoperatively, prednisone, 1 mg/kg daily, was given, tapering to 0.2 mg/kg daily by the fourth or fifth week. Rejection episodes were treated by bolus steroid therapy consisting of 250 to 500 mg of methylprednisolone daily for 3 days. Steroid-resistant rejection was treated with Minnesota equine antilymphocyte globulin (15 to 20 mg/kg daily) for 7 to 10 days, aiming to keep the blood lymphocyte count at 100 to 200 cells/mL. Rejection was diagnosed by a sudden increase in serum bilirubin and aminotransferase levels, accompanied by positive immunologic responses in the recipient.[7] Liver biopsies were performed selectively in patients whose rejection was difficult or impossible to reverse.

Results

The first three patients in the series died of overwhelming fungal infections between 1 and 3 months after transplantation. Two of them (nos. 1 and 3) had bacterial infections following transplantation and required prolonged antibiotic therapy which resulted in fatal opportunistic *Candida* infections. The third patient (no. 2) had an undiagnosed cryptococcal meningitis before transplantation, complicating her liver coma; the

Table II—Data on 11 Survivors of Liver Transplantation

Patient no.	Age, yr	Sex	Disease	Comment
4	26	F	Chronic active hepatitis	Alive and well at 30 mo, at work (radiographer), normal liver function
5	29	F	Chronic active hepatitis	Alive and well at 26 mo, at work (nurse), normal liver function
6	30	F	Biliary hypoplasia and cirrhosis	Alive and well at 22 mo, at work (salesclerk and housewife), normal liver function
7	39	M	Post-necrotic cirrhosis	Alive and well at 18 mo, at work (restaurant manager), normal liver function
9	56	M	Primary biliary cirrhosis	Alive and well at 15 mo, at work (accountant), developed hepatitis B 6 mo after transplant, mild jaundice
10	50	M	Primary biliary cirrhosis	Alive at 13 mo, at home, received two more transplants because of rejection. Now 5 mo after third transplant with normal liver function
11	44	M	Sclerosing cholangitis	Alive at 12 mo, at work (engineer), retransplanted because of rejection, normal liver function
14	14	M	Chronic active hepatitis	Alive at 12 mo, at school, normal liver function
16	34	F	Primary biliary cirrhosis	Alive at 8 mo, at home, chronic rejection and jaundice, will need retransplantation
17	19	F	Hepatoma	Alive at 7 mo, at home, normal liver function
19	48	F	Primary biliary cirrhosis	Alive at 5 mo, at home

Table III—Data on 8 Recipients of Liver Transplant Who Died

Patient no.	Age, yr	Sex	Disease	Survival, d	Cause of death
1	28	M	Massive necrosis, ? toxic hepatitis	58	*Candida* septicemia
2	16	F	Chronic active hepatitis	43	*Cryptococcus* septicemia
3	49	F	Secondary biliary cirrhosis	84	*Candida* septicemia
8	24	F	Chronic active hepatitis	36	Rejection of transplanted liver
12	16	F	Wilson's disease, acute liver failure	102	Rejection of transplanted liver
13	58	F	Primary biliary cirrhosis	73	*Serratia* septicemia
15	29	F	Massive necrosis, acute non-A, non-B, viral hepatitis	9	Reinfection of grafted liver with non-A, non-B, viral hepatitis
18	16	F	Chronic active hepatitis	21	Rejection of transplanted liver

infection disseminated following the operation.

Eleven of the subsequent 16 recipients are currently alive (Table II). Of these 11, 7 have returned to work or school and 4 are convalescing at home (1 has chronic rejection). The patients who have returned to their previous occupation are well and have excellent quality of life. The period of convalescence before patients returned to work or school was usually between 4 and 6 months but was as short as 8 weeks after transplantation.

Four patients received more than one transplant. Patient no. 4, who is alive 2½ years after operation, required a second emergency transplant 9 days after the first because thrombosis of the hepatic artery and liver infarction occurred. She is well at present and has normal liver function. Two patients (nos. 11 and 12) required a second transplant because of rejection. One of them (no. 12) was in extremis at the time of the second transplant and died within 24 hours of the operation. The other patient made a good recovery following the second procedure; he remains well and has returned to work. Patient no. 10 had to be retransplanted twice because of rejection; he is making a satisfactory recovery at home 5 months after receiving his third transplant.

Biliary tract complications developed in three patients (Table IV): a biliary fistula in one and strictures and obstruction at the site of the duct-to-duct anastomosis in two. In each of these patients the biliary drainage was revised to a Roux-en-Y choledochojejunostomy.

Six episodes of acute irreversible rejection occurred in five patients. Three of these patients had another transplant and two are alive. Two patients (nos. 8 and 18) died of rejection and liver failure before another transplant could be done. The overall incidence of irreversible rejection in cyclosporine-treated patients was 30% (six livers lost from rejection in 20 transplants placed in 17 patients).

There have been no long-term survivors in the patients transplanted for acute liver failure from extensive liver necrosis (nos. 1, 12 and 15). These patients were moribund when transplanted and although each of them had immediate recovery with resolution of coma, correction of coagulopathy and reversal of renal failure, they died 9, 58 and 102 days after transplantation (Table III). Patient no. 15, who was transplanted for fulminant, non-A, non-B, viral hepatitis, died when acute massive necrosis and failure of the transplanted liver occurred suddenly 7 days after transplantation. Clinically and histologically, the injury in the grafted liver was similar to that of her original diseased liver.

Serious bacterial infections have been infrequent since cyclosporine was introduced for immunosuppression. Two patients (nos. 3 and 13) in the cyclosporine-treated group had severe bacterial infections that eventually proved fatal. Troublesome viral infections occurred in four recipients in the early postoperative period but eventually resolved. Three patients had mucocutaneous herpes infections and one patient had a cytomegalovirus infection. Three of the four patients who had viral infections required antilymphocyte globulin as part of their immunosuppressive therapy. Hirsutism developed in five patients in the cyclosporine group and two patients had isolated seizures in the immediate post-transplant period. Patient no. 9 suffered from cyclosporine nephrotoxicity and hypertension so the cyclosporine was replaced by Imuran 4 months after transplantation.

The length of stay in hospital following operation is shown in Fig. 1. The mean (± SD) postoperative stay was 52.3 ± 20.3 days with an average of 16.6 ± 18 days in the intensive care unit. Excluding the first three patients in the series, the average length of stay after operation was 50.6 ± 20.4 days, with an average of 11.6 ± 8.0 days in the intensive care unit. The average volume of blood transfused during surgery was 19.6 ± 19 units. Excluding the two patients with the largest and smallest number of transfusions, the average was 16.8 ± 8.9 units.

Of the 19 recipients, 9 required one or more operations in addition to the transplant procedure during the same hospital admission.

Table IV—Surgical Complications in 19 Liver Recipients

Complication	No. of patients
Biliary fistula	1
Biliary stricture	2
Wound dehiscence	2
Postoperative bleeding requiring laparotomy	2
Thrombosis of hepatic artery	1

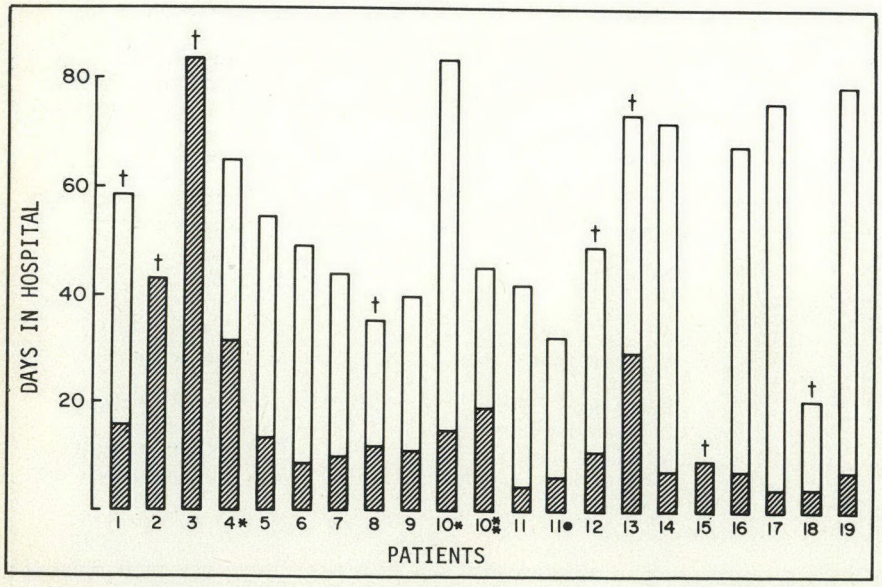


FIG. 1—Postoperative duration of hospitalization for each of 19 liver recipients. Hatched area indicates time spent in intensive care unit. * = transplanted twice during same admission, ** = third liver transplant for this patient, • = second liver transplant for this patient, † = died.

Discussion

The object of liver transplantation is to restore patients with advanced irreversible liver disease to good health and return them to a productive life in the community. Our experience has shown that this is possible for the majority of such patients. Indeed, if this were not possible, the value of liver transplantation would be questionable. The vigour and well-being these patients have enjoyed several months after a successful transplant has been very encouraging. Because we have concentrated our efforts on patients with nonmalignant liver disease, it is anticipated that those who are alive 1 year after transplantation can look forward to many years of worthwhile and trouble-free survival. Unfortunately, most patients who have received a liver transplant for a malignant condition have had recurrent or metastatic disease, and cure is unusual.[8,9] We are not enthusiastic about this indication for transplantation, but some patients with well-differentiated hepatomas appear to be exceptions and may be considered candidates.[10]

Liver transplantation has its major therapeutic role in the management of children with biliary atresia and adults with nonalcoholic cirrhosis, although patients with liver disease in many other

categories may benefit by transplantation.[2,11] In general, candidates should be less than 50 years of age. The timing of transplantation is particularly crucial in patients with cirrhosis. Transplantation needs to be performed before patients reach a terminal stage when severe malnutrition and profound coagulopathy make them unacceptably high operative risks. In hindsight, two of our first three patients were probably too ill to undergo the procedure. On the other hand, the operation should not be recommended too early, when the patient's quality of life and prognosis are still relatively good. Patients with primary biliary cirrhosis are perhaps the best candidates in this respect because clinical deterioration is more progressive and predictable, and choosing a time to intervene can be done more precisely than in some other forms of liver disease. Patients dying of acute liver failure are formidable operative risks for transplantation. The patient and family need to be clearly informed about the risks and benefits of the procedure. It is important for the patient to have a positive attitude and strong self-motivation.

Transplantation for alcoholic cirrhosis may be considered in those rare individuals who have shown their rehabilitation potential and who abstain from alcohol for 6 to 12 months but continue to deteriorate from progression of their liver disease.

The presence of hepatitis B antigenemia is regarded as a contraindication to liver transplantation because of reinfection of the grafted liver.[12,13] The one patient in this series in whom fatal hepatitis developed following transplantation for non-A non-B hepatitis suggests this too should be a contraindication to transplantation.

The time, effort, resources and commitment to run a liver transplant program are substantial. The operation is long, technically demanding and allows little margin for error. Most of the operations are done during off hours so that regular operating-room schedules are minimally disrupted. Operative management is difficult because of the debilitated state of the patient's health and the complexity of metabolic and hemodynamic alterations inherent in the operation. Postoperative care requires balancing the intricacies of immunosuppressive therapy against rejection in patients who are already at special risk of infection. Postoperative complications are frequent. Approximately half the recipients in this series required additional surgery in the postoperative period, an experience similar to that reported by Starzl's group.[14] Long distances may need to be travelled to retrieve donor organs. Patients can expect to spend 6 to 10 weeks in hospital following transplantation, although much of this time is spent in monitoring liver function and adjusting immunosuppression. The blood bank has to be able to respond to sudden and unpredictable demands. An aggressive policy of retransplantation is necessary when irreversible rejection occurs. In spite of these factors and the problems they create, the successes obtained in liver transplantation are extremely gratifying. In patients who have made a good recovery by the time of their discharge from hospital, follow-up care is neither extensive nor a burden and the lifestyle enjoyed by the patients is essentially normal.

Cyclosporine has been a major advance in organ transplantation.[15-17] We have used it in combination with steroids, tapering the steroid dose quickly to low maintenance doses. The selective immunosuppressive effect of cyclosporine on T lymphocytes appears functionally to permit control of rejection without seriously predisposing to bacterial infection. This has special importance for liver recipients who are at high risk of bacterial infections in the early postoperative period. In White's experience[18] and ours, cyclosporine is not an easy drug to use immediately after liver transplantation when hepatic function is stabilizing but abnormal. Absorption, metabolism and excretion of the drug are variable during this period and calculations of the amount of drug needed to maintain therapeutic levels are difficult. Daily adjustment of the dose is required according to serum levels. Levels of recirculating metabolites (detected by radioimmunoassay) can be high and may not correlate with levels of the parent compound (as measured by HPLC assay).[6] The 30% incidence of irreversible rejection in this series reflects these difficulties. In some of the patients immunosuppression was undoubtedly inadequate. We are currently focussing our attention on the HPLC assay of cyclosporine in an attempt to provide ideal immunosuppressive levels of the drug in liver recipients.

In summary, liver transplantation has been used to treat patients with advanced nonalcoholic liver disease. Of 19 patients transplanted, 11 are alive at 5 months to 2½ years after the operation. Three patients required a second and one a third transplant. Rejection is the commonest cause of graft failure and remains a problem despite the use of cyclosporine. In those who survive, the quality of life is excellent.

We are grateful to the many residents, interns, nurses, physiotherapists and other health-care personnel who participated in the care of these patients. The liver transplants could not have been performed without the superb cooperation provided by the staff of the donor hospitals. The technical assistance provided by K. Rycroft, M. Bloch and A. Hellstrom is acknowledged.

References

1. STARZL TE, MARCHIORO TL, VON KAULLA KN, HERMANN G, BRITTAIN RS, WADDELL WR: Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 1963; 117: 659–76
2. STARZL TE, IWATSUKI S, SHAW BW JR, VAN THIEL DH, GARTNER JC, ZITELLI BJ, MALATACK JJ, SCHADE RR: Analysis of liver transplantation. *Hepatology* 1984; 4(1 suppl): 47S–49S
3. DEVINENI R, MCKENZIE N, KEOWN P, KOSTUK W, STILLER C, SILVER M: Cyclosporine in cardiac transplantation. *Can J Surg* 1984; 27: 252–4
4. HARLE IA, GRACE DM, FREI JV, GRANT DR, HUTTON LC, KEOWN PA, STILLER CR: Initial pancreas transplant and attempts to improve pancreatic duct anastomosis. *Transplant Proc* (in press)
5. WALL WJ, CALNE RY, HERBERTSON BM, BAKER PG, SMITH DP, UNDERWOOD J, KOSTAKIS A, WILLIAMS R: Simple hypothermic preservation for transporting human livers long distances for transplantation. Report of 12 cases. *Transplantation* 1977; 23: 210–6
6. CARRUTHERS SG, FREEMAN DJ, KOEGLER JC, HOWSON W, KEOWN PA, LAUPACIS A, STILLER CR: Simplified liquid-chromotographic analysis for cyclosporin A, and comparison with radioimmunoassay. *Clin Chem* 1983; 29: 180–3
7. WALL WJ, STILLER CR, WRIGHT FF, FEINDEL CM, DUFF JH, WALLACE AC: Experimental and clinical liver transplantation. *Transplant Proc* 1982; 14: 724–9
8. CALNE RY: Liver transplantation for liver cancer. *World J Surg* 1982; 6: 76–80
9. IWATSUKI S, KLINTMALM GB, STARZL TE: Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. Ibid: 81–5
10. MACDOUGALL BR, CALNE RY, MCMASTER P, WILLIAMS R: Survival and rehabilitation after orthotopic liver transplantation. *Lancet* 1980; 1: 1326–8
11. CALNE RY (ed): *Liver Transplantation: the Cambridge-King's College Hospital Experience,* Grune, New York, 1983
12. CORMAN JL, PUTNAM CW, IWATSUKI S, REDEKER AG, PORTER KA, PETERS RL, SCHRÖTER G, STARZL TE: Liver allograft. Its use in chronic active hepatitis with macronodular cirrhosis, hepatitis B surface antigen. *Arch Surg* 1979; 114: 75–8
13. VAN THIEL DH, SCHADE RR, GAVALER JS, SHAW BW JR, IWATSUKI S, STARZL TE: Medical aspects of liver transplantation. *Hepatology* 1984; 4(1 suppl): 79S–83S
14. VAN THIEL DH, SCHADE RR, STARZL TE, IWATSUKI S, SHAW BW JR, GAVALER JS, DUGAS M: Liver transplantation in adults. *Hepatology* 1982; 2: 637–40
15. CALNE RY: Organ transplantation and cyclosporin A. *Can J Surg* 1984; 27: 10–3
16. WHITE DJG (ed): *Cyclosporin A: Proceedings of an International Conference on Cyclosporin A: Cambridge, September 1981,* Elsevier, Amsterdam, 1982
17. STILLER CR, KEOWN PA: Cyclosporine therapy in perspective. In MORRIS PJ, TILNEY N (eds): *Progress in Transplantation,* vol 1, Churchill, New York, 1984: 11–45
18. WHITE DJG: Immunosuppression. In CALNE RY (ed): *Liver Transplantation: the Cambridge-King's College Hospital Experience,* Grune, New York, 1983: 201–9

Correction

In the January 1985 issue of the Journal, in the article "Head injuries: a prospective, computerized study" by D. Parkinson, S. Stephensen and S. Phillips, two references, not cited in the text, were omitted from the reference list. On page 80, right-hand column, under the section *"Age"*, the final sentence that begins "In children younger than 9 years..." should read "Head injuries due to traffic accidents occurred most frequently in pedestrians under 9 years of age (54. 2%) and over 70 years (52.4%)." This statement is supported by the following two references: DOWNS AR, BURNS CM: Manitoba accident investigation and accident health care project. Department of Surgery, Faculty of Medicine, University of Manitoba, February 1980, and KALSBEEK WD, MCLAURIN RL, HARRIS BS III, MILLER JD: The National Head and Spinal Cord Injury Survey: major findings. *J Neurosurg* 1980; 53 (suppl): S19-31.

BOOK REVIEWS
continued from page 271

NEW APPROACHES TO THE STUDY OF BENIGN PROSTATIC HYPERPLASIA. Proceedings of the Ninth Brook Lodge Workshop on Problems in Reproductive Physiology, held in Augusta, Michigan, September 26–27, 1983. Edited by Frances A. Kimball, Allen E. Buhl and Donald B. Carter. 394 pp. Illust. Alan R. Liss, Inc., New York, 1984. $56 (US). ISBN 0-8451-0145-5.

This book represents the proceedings of a workshop on problems in reproductive physiology held in 1983. Its contents reflect the varied background of the participants and, although of potential interest to a wide audience, its appeal to the clinician is only modest. The initial chapters on the etiology, anatomy and morphogenesis of benign prostatic hypertrophy are of utmost interest and are replete with new information relevant to individuals dealing with this problem. In addition, the discussion at the end of each chapter is crisp, direct and helpful in understanding the concepts expressed by the authors.

The remaining two thirds of the book are devoted to results of basic research into prostatic hyperplasia in vitro and in animal models. These chapters are highly specialized and are directed towards individuals with expertise in biochemistry and endocrinology. The main interest for the clinical urologist lies in the compilation of current knowledge on the basic aspects of benign prostatic hyperplasia and the assurance that a great deal of interest exists in the elucidation of an aging process, which, according to one of the contributors, may start during puberty! For the basic scientist, on the other hand, there is a wealth of information that updates the present understanding of the pathophysiologic mechanisms involved in the development of benign prostatic hyperplasia that may be manipulated to stop or reverse this process. The inescapable conclusion is that although we have a better understanding of prostate physiology, the means and ways to control the development of prostatic hyperplasia are not yet within our reach.

This volume deserves a place in academic libraries but its usefulness to the clinician is limited.

A. MORALES, MD, FACS, FRCSC

Department of Urology,
Queen's University,
Kingston, Ont.
K7L 2V7

ORTHOPAEDICS. Principles and Their Application. 2 vols. 4th ed. Samuel L. Turek. 1756 pp. Illust. J.B. Lippincott Company, Philadelphia, 1984. $125 (US). ISBN 0-397-50604-X.

The fourth edition of this well-known book on orthopedic surgery is most welcome. Its publication in two volumes, rather than the one volume of the previous edition, allows the use of larger print and thus easier reading. The author has updated it consistent with current knowledge.

Chapter three now includes a discussion of the progenitor cell principle, with discussion of the autoradiographic studies of DNA and RNA. The section on delayed union and nonunion and the use of electric stimulation has been well written. Included here is a consideration of homogeneous and autogenous transplantation. The section on osteonecrosis is also well written. The chapter on collagen pays particular attention to details and the references are complete. The chapter dealing with the blood supply of long bones is new; this is a most important subject and is well covered. Chapter eight has a pertinent addition concerning the biophysical properties of bone and cartilage.

I believe that the short paragraph in chapter 11 on the treatment of old subluxation of the hip should be removed. The new addition on proximal femoral focal deficiency is pertinent.

The chapter on rheumatoid arthritis is well done and informative and has been updated with regard to the use of nonsteroidal anti-inflammatory drugs and immunosuppressive agents. Of extreme value is the inclusion in chapter 14 of the section on compression of the ulnar nerve at the wrist. The material on tumours of bone has been revised to a great extent, with a discussion of new techniques that adds substance to the chapter. Unfortunately, computerized axial tomography as an investigative tool was not considered.

I welcome the addition on the surgical treatment of Paget's disease, discussing the problems of surgical intervention and management.

The author has presented valuable and relevant material on the small blood vessel supply of the upper end of the femur. The section on idiopathic avascular necrosis of the femoral head has been expanded. The chapter dealing with knee ligaments is well documented and has been expanded, giving a description of the methods of assessment and reconstruction of specific ligaments. The section on total knee arthroplasty has also been updated.

I strongly recommend this textbook to the orthopedic surgeon in training and in practice. It is well written and illustrated and it maintains the high standard of the previous editions.

LEON HELLER, MD, FRCSC

Department of Orthopedic Surgery,
The Sir Mortimer B. Davis-
Jewish General Hospital,
Montreal, PQ
H3T 1E2

TEXTBOOK OF DISORDERS AND INJURIES OF THE MUSCULOSKELETAL SYSTEM. An Introduction to Orthopaedics, Fractures and Joint Injuries, Rheumatology, Metabolic Bone Disease and Rehabilitation. 2nd ed. Robert Bruce Salter. 578 pp. Illust. Williams & Wilkins, Baltimore, 1983, $39.75 (US). ISBN 0-683-07500-4.

The second edition of Professor Salter's text is as welcome to this decade of undergraduate students and their teachers as was the original edition. In the foreword, Dr. Paul Curtiss, Editor of the American *Journal of Bone and Joint Surgery,* lists some of the scientific and technical advances that have occurred since the first edition was published 13 years ago. These

continued page 292