KING's FUND CENTRE

King's Fund Forum

Consensus and controversy in medicine

Cancer of the Colon and the Rectum

Programme and Abstracts

18, 19, 20 June
Regents Park College
London NW1

£5.00

CONTENTS

Introduction

24,000 people died of large bowel cancer in Britain last year. Although it is the second most common cancer in the Western World there has been insufficient public recognition of this disease. In spite of major advances in diagnostic and surgical techniques, the last twenty years has seen no improvement in survival which is still less than 30% at 5 years.

Partly for this reason, attention has increasingly turned to primary and secondary prevention. The role of diet in large bowel cancer is still the subject of much research and debate, while in the sphere of secondary prevention the discovery of gene markers provides new possibilities for intervention. At the same time work still continues exploring the use of faecal occult blood tests as a screening tool.

This is a time of enormous uncertainty. Rapid advances in research need to be considered in the context of the patient and current health care systems. This consensus conference is timely, it will allow an opportunity for health professionals, voluntary organisations and the public to share current work, to assess the benefits of current practices and to reflect on the direction of future work for people with cancer of the colon and rectum.

The questions the panel will be asked to address are:

1. Would the detection and treatment of polyps reduce the incidence of cancer of the colon and rectum?

2. Are there other preventative measures which will safely reduce the incidence of cancer of the colon and rectum?

3. How effective are current treatments for cancer of the colon and rectum at improving survival and quality of life?

4. What is the direction of future research?

GENERAL INFORMATION

Conference sessions will all take place in the Tuke's Hall, Regent's College.

Telephone

During the conference, messages can be left for those attending on 01-487 7652

Catering arrangements (in Herringham Hall)

18 June - coffee, lunch and tea

19 June - coffee and lunch

20 June - tea

Microphones

Speakers from the floor are asked to use the aisle microphones and to identify themselves by names and affiliation.

Consensus Statement

The final statement will be sent to all participants after the conference.

CONFERENCE PROGRAMME

CHAIRMAN: Professor Ross Anderson, Head of Department of Public Health Sciences, St George's Medical School, London

18 June 1990

9.00	Introduction	Barbara Stocking, Director King's Fund Centre
9.15	An epidemiological overview	Sir Richard Doll, Emeritus Professor of Medicine, University of Oxford

I The polyp cancer sequence - is it irrefutable?

09.35	The polyp cancer sequence	Professor Nick Wright, Director, Histopathology, Department, Hammersmith Hospital
09.55	Polyps and cancer risk	Dr Phillip Quirke, Hon Consultant Pathologist, University of Leeds
10.15	Is polypectomy worthwhile?	Dr Christopher Williams, Consultant Physician, St Mark's and St Bartholomew's Hospital, London
10.35	Discussion	
11.05	COFFEE	

II Intervention strategies

11.25	Intervention strategies and their evaluation	Professor Nicholas Wald, Head of Department of Environmental and Preventive Medicine, St Bartholomew's Medical College, London

Primary prevention

11.45	The diet debate	Dr Peter Boyle, Head, SEARCH Programme, International Agency for Research into Cancer, Lyon
12.05	The role of fat	Dr Michael Hill, Deputy Head, Pathology Division, Public Health Laboratory Service, Porton Down, Wilts
12.25	Starch and fibre	Dr Sheila Bingham, MRC Scientist, The Dunn Nutrition Centre, Cambridge

12.45	Discussion	
13.05	LUNCH	
	Secondary prevention	
14.05	Principles and approaches to screening	Dr Howard Cuckle, Reader in Preventive Medicine and CRC Fellow, St Bartholomew's Medical College
	Genetics	
14.25	Genetics and cancer risk	Mr Malcolm Dunlop, MRC Clinical Scientist, Department of Clinical Surgery, Royal Infirmary, Edinburgh
14.45	Screening high risk groups	Dr Victoria Murday, Consultant Clinical Geneticist, Leeds General Infirmary
15.05	Discussion	
15.20	TEA	
	Faecal occult blood tests	
15.40	The yield and benefits	Professor Jack Hardcastle, Head of Department of Surgery, Queen's Medical Centre, Nottingham
16.00	The risks and costs	Dr Petr Skrabanek, Lecturer in Community Health, Trinity College, Dublin
16.20	Discussion	
16.30	The economics of Screening	Mr Andrew Walker, Research Assistant, Department of Surgery, Queen's Medical Centre, Nottingham
16.50	Implications for health care organisations	Mr Ron Akehurst, Director, Health Economics Consortium, University of York
17.10	Discussion	
17.45	Close of day	

19 June 1990

III Quality of care

09.00	The patient's view	Mr W C Reynolds, Member, British Colostomy Association
	Treatment	
09.15	Treatment of advanced disease	Dr Richard Begent, Reader in Medical Oncology, Charing Cross Hospital, London
09.30	Liver resection in advanced disease	Mr Myrddin Rees, Consultant Surgeon, Basingstoke District General Hospital
09.48	Adjuvant radiotherapy in rectal cancer	Dr Sid Arnott, Consultant Radiotherapist, St Bartholomews Hospital. London
10.00	Adjuvant chemotherapy for colon and rectal cancer	Professor Irving Taylor, Professor of Surgery, Southampton and Royal South Hants Hospital
10.20	Discussion	
11.35	COFFEE	
	Survival	
10.55	International variations in survival rates	Dr Tom Davies, University Lecturer in Community Medicine, Addenbrookes Hospital, Cambridge
11.10	Clinical factors that influence outcome	Mr Robin Phillips, Consultant Surgeon, St Bartholomew's Hospital, London
11.30	Discussion	
	Quality of life	
11.40	Is follow-up worthwhile?	Mr Geoffrey Oates, Consultant Surgeon, The General Hospital, Birmingham
11.55	The use of outcome measures in cancer of the colon and rectum	Dr Sam Ahmedzai, Consultant in Palliative Medicine, the Leicestershire Hospice
12.15	Nursing care	Mrs Celia Myres, Clinical Nurse Specialist (Stoma Care), St Marks Hospital, London

12.35 Discussion

12.45 OPEN SESSION

13.30 LUNCH

20 June 1990

Final Session

13.00 The draft consensus statement will be available to the audience

13.30 Presentation of consensus statement and discussion with audience

14.45 Close of conference

TEA

16.00 The final consensus statement will be made available

16.15 PRESS CONFERENCE

PANEL MEMBERS

Professor Ross Anderson graduated in medicine from Melbourne University. He is currently Professor of Clinical Epidemiology and Social Medicine, Chairman of Department of Public Health Sciences, St George's Hospital Medical School, London. Professor Anderson's research interests include: the epidemiology and medical care of asthma and chronic respiratory disease, perinatal epidemiology, and health consequences of solvent (volatile substances) abuse. He has written and edited many books and articles on these subjects.

Dr Priscilla Alderson is a Researcher in the sociology of healing, at the Community Paediatric Research Unit, Department of Child Health, Westminster Children's Hospital, London. The subject of her Phd thesis, from Goldsmith's College in 1987, was on 'Informed consent: Parents' consent to paediatric cardiac surgery'. Dr Alderson has written several booklets for various voluntary organisations and articles for professional and popular journals. She is currently Hon Secretary and newsletter editor of CRES (Consumers for Ethics in Research). She also speaks at course and conferences for health professionals and sociologists on children and on limitations of conventional medical ethics.

Professor Tim Cooke graduated in medicine from the University of Liverpool in 1973. He is currently a St Mungo Professor of Surgery at the Glasgow Royal Infirmary. He was awarded the Hunterian Professorship by the Royal College of Surgeons of England in 1980; the Registrar Research Prize of the Liverpool Medical Institute in 1979; and a Helen Tompkinson - BMA Cancer Research Scholarship in 1981. Professor Cooke is a member of the Colorectal Cancer Group.

Dr Alan Davison is District General Manager at the North East Essex Health Authority. He has had extensive managerial experience in both teaching and non-teaching district health authorities. Dr Davison has an Honours Degree in French from the University of Leicester and has the professional examinations of the Institute of Health Service Management. The subject of his PhD thesis from Brunel University was information and budgeting for medical staff.

Dr Lesley Fallowfield trained as a nurse at Guy's Hospital, London. In 1980 she gained her BSc(Hons) in Experimental Psychology from Cambridge University. She is currently Senior Lecturer in Health Psychology at the London Hospital Medical School, and Honorary Lecturer in Psychology, King's College Hospital, London. Dr Fallowfield is Co-Editor of the British Psychosocial Oncology Group Newsletter.

Mr Hugh Gravelle is Reader in Economics, Queen Mary and Westfield College, London. He was Economic Advisor to the Royal Commission on the National Health Service. His main research interests are in the economics of law and in the microeconomics of the public sector. His work in health economics has included: the relationship between unemployment and health, the evaluation of screening for breast cancer, health service professions and the analysis of health care insurance.

Dr Susan Huson graduated in medicine from the University of Edinburgh. She is currently Consultant Clinical Geneticist, at the Churchill Hospital, Oxford. Her interests in cancer genetics include: dominantly inherited family cancers, and in particular, neurofibromatosis.

Dr Margaret Lloyd is Senior Lecturer in General Practice at the Royal Free Hospital School of Medicine, London. Her research interests include: the interface between primary and secondary care, alcohol-evaluation of health education and advice for hazardous drinkers, and the development of outcome measures for use in general practice.

Dr Kath Melia is a Lecturer in the Department of Nursing Studies at the University of Edinburgh. Dr Melia's interests include: nursing sociology, qualitative research methods, and health care ethics. She is the author/co-author of several books on nursing ethics and the occupational socialisation of nurses.

Mr Neil Mortensen graduated in medicine from the University of Birmingham. He has been Senior Registrar at St Marks Hospital, and was formerly Consultant Senior Lecturer in the University Department of Surgery, Bristol. He is currently Consultant Colorectal Surgeon at the John Radcliffe Hospital, Oxford. He has written and edited numerous publications and chapters on colorectal cancer, and is co-editor of the International Journal of Colorectal Disease. His particular interests in colorectal cancer are staging, endosonography, and sphincter saving surgery.

Dr Robert Newcombe is Senior Lecturer in Medical Statistics at the University of Wales College of Medicine. He was awarded a PhD degree for a thesis evaluating risk assessment in pregnancy. He is involved in teaching the basic concepts and methods of statistics as applied to clinical practice, epidemiology and research, to medical and dental undergraduates and a wide range of groups of postgraduates in the health-related field, including public health specialists and postgraduates from overseas. Dr Newcombe's research interests include: the appropriate application of statistical methodology to improve the standard of planning, analysis and publication of research studies.

Ms Fedelma Winkler is Director of Service Planning and Service Development at Barking and Havering Family Practitioner Committee. Much of her contribution to the Consensus Conference debate will be based on her work at City and Hackney Community Health Council where she was until recently Director, Greater London Association of Community Health Councils. Ms Winkler's particular interest is in the way in which communities can be involved in health care decision making. She has written widely on consumerism and health care.

SPEAKERS:

Dr Sam Ahmedzai graduated in medicine from the Universities of St Andrew's and Manchester in 1976. Dr Ahmedzai was appointed Director and Honorary Consultant Physician at the Leicestershire Hospice, and Associate Director of the Trent Regional Palliative and Continuing Care Centre in 1985. He is Chairman of a Study Group on Quality of Life, for the European Organisation for Research and Treatment of Cancer, and Chairman of the Research Committee of the European Association for Palliative Care. Dr Ahmedzai's main areas of research are quality of life evaluation, palliation of symptoms, and computer-aided decision making in medicine.

Mr Ron Akehurst has been Director of the York Health Economics Consortium at University of York, since April 1986. Prior to that he was a Senior Research Fellow in the Economic Aspects of Clinical Practice at York, which involved running training courses for clinicians in economics throughout the north of England. Earlier experience included seven years as Lecturer at the University of Lancaster, and two years as Economic Advisor to the DHSS. Mr Akehurst's main research interests are in the application of economics to assist NHS managers in their planning decisions.

Dr Sidney Arnott graduated in medicine from the University of Edinburgh in 1962. He is currently Consultant Radiotherapist at St Bartholomew's Hospital and was previously Senior Lecturer in Clinical Oncology at the University of Edinburgh. Dr Arnott is an Examiner to the Royal College of Surgeons, Member of the Council of the Royal College of Radiologists, Scientific Secretary and Member of the Working Party of the Medical Research Council on rectal cancer and Member of the Working Party on Neutron Therapy of the Medical Research Council. His main research experience has been in gastrointestinal tract cancers and the use of fast neutrons in the treatment of a wide variety of malignancies.

Dr Richard Begent is Reader in Medical Oncology at Charing Cross and Westminster Medical School, Honorary Physician at Charing Cross Hospital and Gibb Research Fellow of the Cancer Research Campaign. He qualified at the Medical College of St Bartholomew's Hospital and has held posts at St George's Hospital, the Royal Marsden Hospital and the Imperial Cancer Research Fund. Present interests include the location and treatment of recurrent colorectal cancer and a laboratory and clinical research programme on antibody targeted therapy of cancers of the colon and rectum.

Dr Sheila Bingham is a member of the Scientific Staff of the Medical Research Council's Dunn Nutrition Unit, Cambridge. Her present research interests include the epidemiology of diet and large bowel cancer, the use of microcapsules for in vivo monitoring of mechanisms of diet in colorectal cancer, and the metabolism of plant oestrogens in the large gut. She is also a joint investigator in a proposed European prospective collaborative study of diet and cancer. She is the author of a recent Health Education Authority briefing paper on Diet and Cancer for health professionals. She is currently participating in a number of Department of Health's advisory groups to COMA on Nutritional Surveillance.

Dr Peter Boyle is Head of the SEARCH Programme at the International Agency for Research into Cancer at Lyon.

Dr Howard Cuckle was educated at the Universities of Leeds and Oxford. He is currently Reader in Preventive Medicine and CRC Fellow at St Bartholomew's Medical College. Since 1975 he has worked in the field of epidemiology and preventive medicine at Oxford, Tel Aviv and London. Dr Cuckle's research interests include: screening for cancer in adults, and antenatal screening for congenital abnormalities. In the field of screening, his main contributions have been in the development of the scientific basis of alpha-fetoprotein screening for neural tube defects and Downs syndrome, and the subsequent diagnostic amniotic fluid tests.

Dr Tom Davies qualified in medicine at the London Hospital Medical College. He is currently University Lecturer in the Department of Community Medicine at the University of Cambridge; Honorary Specialist in Public Health Medicine at the East Anglian Regional Health Authority; and General Director of the East Anglian Cancer Registry. Dr Davies has published a number of articles including his research into undescended testis and cancer of the testis.

Sir Richard Doll qualified in medicine at St Thomas's Hospital Medical School, University of London, in 1937. He was appointed Regius Professor of Medicine, University of Oxford in 1969 and Head of Green College, Oxford in 1979. Sir Richard directed the Cancer Epidemiology and Clinical Trials Unit at Oxford, and has continued to work with the Imperial Cancer Research Fund as Honorary member of the Cancer Studies Unit since his retirement. Sir Richard's work has included studies of the causes and treatment of peptic ulcers, causes of lung cancer and leukaemia, occupational hazards of cancer, the effects of smoking, exposure to ionizing radiations and the use of oral contraceptives.

Mr Malcolm Dunlop is an MRC Clinical Scientist in the Department of Clinical Surgery at the Royal Infirmary, Edinburgh. His particular interests are the molecular genetics of familial adenomatous polyposis and colorectal cancer.

Professor Jack Hardcastle graduated from Emmanuel College, Cambridge, the London Hospital Medical School and University of London. He is currently Head of Department of Surgery, University of Nottingham. Professor Hardcastle is a Member of the Council of the Royal College of Surgeons of England, Chairman of the Colorectal Sub-Committee of the United Kingdom Coordinating Committee for Cancer Research, a Member of the Scientific and Education Committees of the Cancer Research Campaign, a member of the Department of Health's Standing sub-Committee on Cancer, and a Member of the WHO Collaborating Centre for Prevention of Colorectal Cancer.

Dr Michael Hill is Deputy Head of the Pathology Division of the Public Health Laboratory Service at Porton Down, Wiltshire, and Honorary Consultant to the Research Department of St Mark's Hospital, London. His main research interests include: the metabolic activities of the intestinal microbial flora, particularly with respect to their possible role in the causation of human gastrointestinal cancers.

Dr Victoria Murday graduated in medicine from the London Hospital Medical School. Her initial training was in paediatrics and later in clinical genetics. She was a Clinical Research Fellow for the Imperial Cancer Research Fund. Dr Murday is currently Consultant clinical Geneticist for the Yorkshire Region based at Leeds General Hospital.

Mrs Celia Myres trained as an SRN in 1968 and gained her Stoma Care Certificate in 1977. She was Ward Sister at the Good Hope Hospital, Sutton Coldfield for 12 years where she was involved in setting up a Stoma Care Unit in 1973, and Stoma Care Nurse at St Thomas's Hospital for 5 years. Mrs Myers is currently Clinical Nurse Specialist in Stoma Care at St Marks Hospital, London.

Mr Geoffrey Oates graduated in medicine from the University of Illinois. He is currently Consultant in Surgical Oncology and General Surgery at the General Hospital, Birmingham, and Senior Clinical Lecturer in Surgery at the University of Birmingham. Mr Oates is the Scientific Secretary of a Working Party on Rectal Cancer for the Medical Research Council; a member of the Colorectal Sub-Committee, UK Coordinating Committee for Cancer Research; and President of the Association of Coloproctology of Great Britain and Ireland.

Mr Robin Phillips is Consultant Surgeon at St Mark's Hospital and Senior Lecturer, Honorary Consultant Surgeon at the Medical College of St Bartholomew's Hospital. Mr Phillips completed his Higher Surgical Training at the Royal Free and St Mary's Hospitals. The subject of his MS thesis was 'Clinical and experimental studies in colorectal cancer: Local recurrence and the effect of sutures on tumour induction'. His research interests include: aetiology of colorectal cancer, familial adenomatous polyposis, anastomotic recurrence of disease, and the interaction of anastomosis/cancer/radiotherapy. He has written extensively on these subjects.

Dr Philip Quirke graduated from Southampton University in 1980. He was a Lecturer in the Department of Pathology at the University of Leeds for eight years until his appointment as Honorary Consultant/Senior Lecturer, Department of Pathology, University of Leeds, earlier this year. The subject of Dr Quirke's PhD theses in 1987 was colorectal carcinoma. His interests include: gastrointestinal neoplasia and molecular pathology, and his current research interests in colorectal neoplasia are in the detection of ras and P53 and prediction of local recurrence by pathological techniques.

Mr Myrddin Rees qualified in medicine at Westminster Hospital in 1973. His surgical training was gained at St George's Hospital, a two year Fellowship at the Ochsner Clinic, New Orleans, USA, and liver surgery training under Professor Johannes Scheele at Erlangen University, West Germany. Mr Rees is currently Consultant Surgeon at Basingstoke Hospital.

Mr W C Reynolds is a retired Civil Servant. In 1984 Mr Reynolds underwent surgery for the removal of a cancer of the rectum. A year later he joined the British Colostomy Association as a Patient Visitor, helping to counsel people with colostomies.

Dr Petr Skrabenek is a Senior Lecturer in Community Health at Trinity College, Dublin. Until 1968 he was a Forensic Toxicologist in Czechoslovakia He gained his medical degree in Ireland in 1968. For the past six years his work has been concerned with cancer prevention and screening. Dr Skrabenek has published many articles and is author/co-author of six books - the most recent in 1989, 'Follies and fallacies in medicine'.

Professor Irving Taylor is Professor of Surgery at the Southampton and Royal South Hants Hospital

Professor Nicholas Wald is Head of the Department of Environmental and Preventive Medicine at St Bartholomew's Medical College, London.

Mr Andrew Walker graduated from University College, London with a BSc degree in economics. In 1987 he completed an MSc in health economics at York University. His particular interests are the economics of screening and in costing hospital activity.

Dr Christopher Williams is Consultant Physician, specialising in gastrointestinal endoscopy at St Mark's Hospital for Diseases of the Colon and Rectum and St Bartholomew's Hospital, London, with attachments to the Hospitals for Sick Children and others. Since 1970 he has become experienced in most forms of GI endoscopy but particularly in colonoscopy and colonoscopic polypectomy, a field in which he has taught, published and lectured widely. He is committee member and Endoscopy Vice President of the British Society of Gastroenterology. Current interests include paediatric endoscopy, teaching and television teaching of colonoscopy, development of computerised endoscopy stimulators and the application of microcomputers to endoscopic practice.

Professor Nick Wright has been Professor of Histopathology at the Royal Postgraduate Medical School since 1980. Before that he was at Newcastle and Oxford. In addition, he is also Associate Director (Clinical Sciences) at the ICRF. His interests include gastrointestinal pathobiology and epithelial cell biology.

PLANNING COMMITTEE

Professor J Chamberlain, Regional Cancer Organisation, Royal Marsden Hospital

Dr D Costain, Director - Acute Services Programme, King's Fund Centre for Health Service Developments

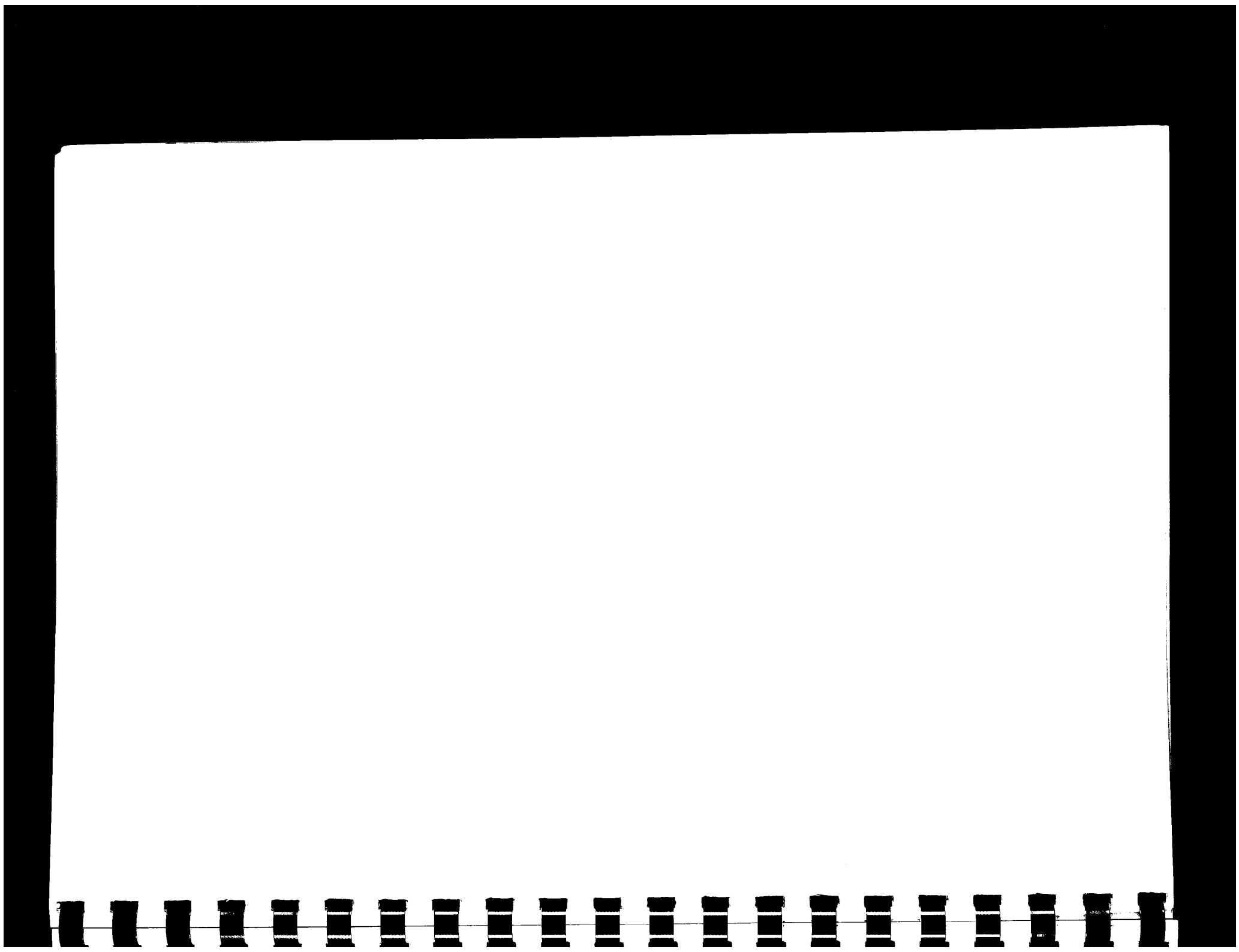
Dr R James, Radiotherapy Department, Christie Hospital and Holt Radium Institute, Manchester

Mr J Northover, Consultant Surgeon, St Mark's Hospital, London

Dr Allyson Pollock, King's Fund Fora Conference Coordinator, King's Fund Centre for Health Services Developments

Ms B Stocking, Director, King's Fund Centre for Health Service Developments

Dr Julia Verne, Research Fellow, Cancer Research Fund, St Mark's Hospital, London



ABSTRACTS

EPIDEMIOLOGY OF CANCER OF THE LARGE BOWEL

Sir Richard Doll

Tumours of the large bowel are conventionally divided into tumours of the colon and rectum. Aetiologically, both have much in common and, in so far as there are differences in aetiological factors, they are not distinguished sharply at the colo-rectal junction. For much of this paper tumours of the large bowel, are, therefore, regarded as a single entity.

Data from two Cancer Registers that have achieved almost complete registration show that for colon cancer the male and female rates are almost identical at all ages, but that for rectal cancer the male rates are mostly higher. In each case the male rate increases with age more rapidly and by 70-74 years of age the male rate for rectal cancer is twice the female rate.

Experience of other epithelial cancers suggests that exposure to the principal aetiological agents evenly from birth causes a rate of increase that is approximately proportional to the fourth power of age and that a sharper rate of increase indicates that exposure to such agents begins only later in life. Colon and rectal cancer in women both increase in incidence with a power of age that is only slightly greater than 4 but both types of cancer increase more sharply in men. This implies that exposure to the principal aetiological factors begins soon after birth, but that men begin to be exposed to some additional factor later.

The age-specific rates for colon cancer diverge upwards from a linear relationship early in life, due to the incidence of tumours in young people affected by familial adenomatous polyposis.

These characterictics vary little from place to place, although there is a substantial difference in the overall incidence of the disease. The difference is most marked between the blacks in Africa and some Asiatics and populations of the developed countries of Australasia, Europe, and North America. This led Denis Burkitt to propose that the principal cause of the high rates was the processing of cereals and the consequent removal of fibre from the diet. Burkitt's conclusions were based on clinical series, but some good incidence figures have subsequently been obtained which confirm the reality of the difference.

The most reliable comparisons are limited to incidence rates in middle age, as the medical services for old people in undeveloped countries are either defective or relatively unused. Figures for cancers of the whole large bowel in black Africans and Asians are, therefore, shown in Table 1, limited to ages 35 to 64 years, to which are added some figures from South America.

The Table shows that low rates are not confined to Africa and Asia, and that Asiatic rates are not all low. Several are less than a fifth of the highest. Table 2 shows that large differences are recorded for Japanese, Chinese and black and white populations, when they live in different socio-economic circumstances, so that the differences are not genetic in origin.

For comparisons within developed countries the use of rates limited to middle ages is less appropriate, as the greatest burden of the disease falls on older people and the recorded rates are reliable up to 75 years of age. Cumulative incidence rates up to 75 years are, therefore, shown for some such populations in Table 3. These are the sums of the incidence rates at different ages and indicate the approximate percentages of people who would develop the disease in the absence of other causes of death. Estimated rates are also included for Bulgaria, Greece, Poland, Romania and Spain based on their mortality rates and derived on the assumption that the ratio between the cumulative incidence rate and the age standardized mortality is the same as the average for elsewhere. The closeness of the observed and estimates rates validates the recorded incidence data. Evidently, cancer of the large bowel is only about a third as common in Poland, South-East Europe, and Spain as it is in Australia, New Zealand and the USA.

Like all common types of cancer, the incidence also varies with time. The trend is not, however, easy to establish.

First, the recorded trend may be distorted by variation in the efficiency of registration and by the spread of screening, which brings tumours to attention that might not present clinically for years. Both are liable to produce an appearance of increasing incidence. Screening may not have had much effect on recorded rates in Britain, but improving registration has. Even now the national figures are too low. In these circumstances it is helpful also to

examine trends in mortality, although they are also affected by improvements in therapy.

Secondly, the trends may vary with age, as the incidence of the disease in old age is partly determined by changes in behaviour and the prevalence of carcinogenic agents in the distant past, whereas the trends at younger ages can have been determined only by the changes that have occurred more recently. We can, therefore, assess the effects of recent changes in society only by examining the trends in the relatively young.

Table 4 shows both the trends in age-specific mortality rates from 1951 and the trends in the nationally recorded age-specific incidence rates since 1971. The results indicate: (i) an increase in the efficiency of cancer registration, (ii) a reduction in incidence at young ages that has more than compensated for more complete registration, and (iii) a reduction in fatality that began in the late 1950s. The reduction is too great to be due to the prophylactic treatment of people with familial adenomatous polyposis and suggests that there has been a reduction in the prevalence of causative agents in the last 20 years.

Minor factors identified by epidemiological observations that are not discussed by others may be a sedentary life in the case of colon cancer, beer drinking in the case of rectal cancer, and schistosomiasis in China in both.

THE ADENOMA-CARCINOMA SEQUENCE

Professor Nicholas Wright, Hammersmith Hospital

Crystallisation of a large amount of evidence, clinical, epidemiological and histopathological, indicates that, excluding ulcerative colitis, carcinoma of the colon arises from a pre-existing adenoma. The alternative viewpoint, that of de novo carcinoma, orginating from pristine, normal mucosa, is vanishingly rare; most reported instances are based on a misconception of what an adenoma actually is.

Having said this, what is the risk of any adenoma progressing to carcinoma? Despite many attempts at more sophisticated analysis, viz mucin histochemistry, flow cytometry and DNA analysis, the best predictors of progression remain clinico-pathological: the type of adenoma (tubular, tubulo-villous or villous, in that order), the size, the degree of atypia or dysplasia, and the number of adenoma are the most effective prognostic indicators. Using these data, a model for treatment/follow-up can be proposed on the basis of these findings.

Patients with multiple adenomas, tubulo-villous adenomas or villous adenomas with moderate to severe dysplasia should be followed up by colonscopy. The problem remains, how often?

POLYPS AND CANCER RISK

Dr Philip Quirke, University of Leeds

I have been asked to address three questions. Firstly, what is the prevalence of adenomas by age, sex and site and how does this compare to colorectal cancer? Secondly, what is the prevalence of undiagnosed carcinoma of the colon and how does this compare to the prevalence of clinically diagnosed carcinoma and screened carcinoma? Lastly, what happens to polyps left *in situ* on follow-up and what are the clinical recovery rates of adenomas?

The reported prevalence and frequency of colorectal neoplasia depends on a wide range of variables unconnected to the lesion itself. When assessing the value of a study many factors should be taken into account as shown in Table 1.

Table 1

Factors to be addressed in studying the value of pathological or surgical epidemiological studies

Prospective or retrospective study
Geographical area of population
Racial, age and sex distributions
Subpopulations selected for study
(i) Asymptomatic
(ii) Symptomatic
(iii) Referred adenoma case
(iv) Referred carcinoma case

Method of detection used in study
- (i) Proctoscopy
- (ii) Sigmoidoscopy
- (iii) Flexible sigmoidoscopy
- (iv) Colonoscopy
- (v) Barium contrast X-ray study
- (iv) Autopsy study

Confirmation of neoplasm
- (i) Visual
- (ii) Histopathology
  - (a) Diagnostic criteria
  - (b) Interobserver variation
  - (c) Minimum size criteria

For adenoma prevalence properly conducted prospective, histopathologically controlled Autopsy Studies are the gold standard against which other methods should be matched. There are many good studies which are shown in the appendices, but where possible UK reports will be utilised.

Autopsy studies

Adequate histologically controlled, prospective studies on substantial numbers of cases are available from several countries. The prevalence of colorectal adenomas varies from almost absent (Africa: eg Burkitt; (Williams et al; Clark et al); to very low (India: Bhargava & Chopra), moderate (Finland) to high (UK Chapman, USA Rickert). UK studies from Liverpool (Williams et al) and Aberdeen (Clark et al) found adenomas in 36.9% and 39% of males and 28.7% and 30% of females. Adenomas increased in frequency with age as shown in Table 2 as did the frequency of the presence of more than one adenoma (Appendix).

	Male		Female	
	Liverpool	Aberdeen	Liverpool	Aberdeen
<54	20%	16%	14.8%	4%
55-64	34.1%	32%	20.0%	18%
65-74	43.9%	44%	35.3%	40%
75+	52.4%	64%	32.8%	48%
Total group	36.9%	39%	28.7%	30%

Liverpool n=365 Aberdeen n=200

Table 2 Adenoma by age and sex

Adenomas are relatively evenly spread throughout the colon and do not show the marked left sided bias of carcinomas. In the Aberdeen autopsy study (Clark et al) 28% of adenomas were found in caecum and ascending colon, 28% in the transverse, 15% in the descending, 21% in the sigmoid and 8% in the rectum. However, adenomas arising in patients with adenocarcinoma show a distribution more akin to that of carcinomas with an increased number of left sided lesions (Ekelund & Linstrom). Thus in individuals who pass through the whole spectrum of colorectal neoplasia their adenoma distribution approaches that of adenocarcinoma. If arising in association with a carcinoma adenomas are seen most frequently in the same segment of the colon ie transverse colonic carcinomas most frequently have transverse polyps so adenomas are most often present in the local vicinity of the tumour (Ekelund & Lindstrom). When multiple

adenomas occur they cluster together more often than would be expected by chance (Eide & Schweder). A marked change in adenoma distribution is seen with age with left sided polyps found predominantly in younger patients and right sided polyps in elderly patients. This mirrors the reported increase in incidence of right sided cancers in elderly patients (Slater et al).

Adenocarcinoma

Adenocarcinoma presents most commonly between the age of 70 and 75. The male:female ratio is 1.3:1 in Liverpool and New York which is identical to adenomas in these areas. (range in studies 1.0-1.56:1). The detailed breakdown of site for adenocarcinoma and adenoma given by Clarke et al, together with the distribution of adenomas found in carcinoma patients (Ekelund & Linstrom) are given in Table 3.

Autopsy studies have reported 3.0%, 2.2% and 1.6% of cases to have invasive carcinoma, usually of an earlier stage than those seen in a symptomatic population. 11 of 22 (50%) cancers reported were Dukes Stage A, 5/22 (23%) Dukes B and 6/22(27%) Dukes Stage C. In one large Italian series (Delendi et al) undiagnosed colorectal cancer which was not the cause of death had a similar site distribution to cases presenting to surgeons whereas undiagnosed colorectal carcinoma proving to be the cause of death was more frequent in the right, transverse or descending colon. The incidence was 9.6 adenocarcinomas per 1000 autopsies

ranging from 3.9 per 1000 for men aged 40-49 years to 15.9 per 1000 for men over 80+ years. One large screening study (Hardcastle et al) found an increase in carcinomas of the sigmoid colon in the screened group but the control group showed the same distribution of colorectal carcinomas as other studies with 74% occurring in the sigmoid or rectum.

Colonoscopy studies

Colonoscopy studies (Konishi & Morson, O'Brien et, Gillespie et al) confirm autopsy study findings but tend to underestimate the number of right-sided adenomas.

Table 3 Distribution of adenomas, adenomas in association with adenocarcinoma and adenocarcinomas

	Adenoma (Clark et al)	Adenoma in association with adeno-carcinoma (Ekelund & Lindstrom)	Adenocarcinoma
Caecum and ascending	28%	36.5%	20%
Transverse	28%	11.7%	13%
Descending	15%	9.3%	5%
Sigmoid	21%	21.8%	23%
Rectum	8%	20.3%	39%

Age distribution of adenomas autopsy studies (1)

Percentage of cases with histologically verified adenomas

	Williams n = 365 Liverpool			Clark *et al* n = 200 Aberdeen		Kupio		Tromso	
	M	F		M	F	M	F	M (prior to regrading)	F (prior to regrading)
<54	20	14.8	20-54	16	4	4	8	15 (24)	21 (37)
55-64	34.1	20.0	55-64	32	18	17	0	17 (28)	15 (15)
65-74	43.9	35.3	65-74	44	40	4	23	40 (47)	14 (18)
75+	52.4	32.8	75+	64	48	16	11	45 (51)	41 (45)
TOTAL	**36.9**	**28.7**	TOTAL	**39**	**30**	**10**	**11**	**32** (40)	**24** (33)
Ratio	1.28:1		Ratio	1.3:1		1.1:1		1.3 : 1	

Quirke P., 1990

Age distribution of adenomas autopsy studies (2)

Percentage of cases with histologically verified adenomas

Chapman n = 443			Feyter n = 1,800			Rickert n = 518			Blatt n = 446			Vatn & Stalsberg : n = 445		
	M	F		M	F		M	F		M	F	T		M	F
35-44	33	16.6	35-44	17.6	9.9	<50	21.9	12.1	30-39	0	0	0	-	-	-
45-54	45	20	45-54	40.1	21.4	50-54	40.6	22.2	40-49	12	23	20	<50	6	7
55-64	43	37	55-64	57.8	31	55-59	33.3	41.9	50-59	46	22	34	50-59	21	28
65-74	65	37	65-74	64	37.1	60-64	47.8	50.0	60-69	35	37.5	36	60-69	36	19
75-87	63	50	75-87	67.9	56	65-69	70.6	48.0	70-79	45	46	44	70-79	53	35
						70-74	67.4	50.0	80-89	51	40	45	80+	52	43
						75-79	67.7	29.2	90-99	0	40	25			
						80+	61.1	63.0							
						Total	**52.8**	**38.4**					Total	**34**	**32**

Ratio 1.38 : 1

Attwater & Bargan
No histological control, overall prevalence 69%, did not distinguish hyperplastic polyps.

Quirke P., 1990

Age distribution autopsy studies 3

Arminski & Mclean (1964) n = 330

	M	F	T
20-29	0	22.2	14.3
30-39	35.3	13.6	23.1
40-49	13.1	24.2	18.7
50-59	23.9	30.8	26.9
60-69	39.9	25.3	34.3
70-79	46.1	47.3	46.5
80+	46.3	42.5	44.4
Total	**34.5**	**31.5**	**33.0**

Africa

Bremner & Ackerman
0/1000

Parker & Skinner
0/13,000

Huitt & Templeton
0/2000

Distribution of adenomas autopsy studies (1)

Percentage adenomas by site

	[1]All	[2]All	[2] <5mm	[2] 5-9mm	[2] 10+mm	[3]All	[3] >7mm	[3]Ca	[4]All	[5]All	[5] <5mm	[5] 5-9mm	[5] 10+mm
Caecum	8.4	4.9	33	41.7	25.0				3.5	12.5	33.7	48.2	18.1
†Caecum + ascending colon						28	36	20					
Ascending	15.6	16.9	43.9	48.8	7.3				21.4	26.2	43.7	40.1	16.2
Transverse	21.1	35.5	47.7	41.8	10.5	28	14	13	29.6	27.8	46.0	43.1	10.9
Descending	4.7	12.3	33.3	56.7	10.0	15	15	5	14.2	9.1	43.1	43.1	13.8
Sigmoid	21.9	16.9	41.5	39.0	19.5	21	26	23	22.1	17.3	41.8	42.8	16.4
Rectum	18.8	13.2	40.6	43.8	15.6	8	9	39	8.9	7.1	48.9	29.8	21.3

[1] Arminski & McLean 1964, n = 1000 Michegan, U.S.A.
[2] Williams et al 1982, Liverpool n = 365
[3] Clark et al 1985 Combined figure for Aberdeen and Tromso and Cancer Registry data
[4] Eide and Stalsberg
[5] Rickert et al 1979. n = 518 New York U.S.A.
† Where combined figures only are given

Right sided tumours Slater *et al*

Changing distribution of carcinoma of the colon and rectum

	1945-49	1956-57	1966-69	1976-78
Caecum	11.4	12	10.7	17.8
Ascending	3.8	6.3	5.0	4.1
Transverse	12.5	17.0	10.0	15.6
Descending	5.0	4.0	6.5	3.4
Sigmoid	29.3	33.7	42.2	33.4
Rectum	37.7	31.4	24.3	25.4

Hoff et al.

Polyps <5mm left *in situ* for 2 years

Year	Polpys showing growth n = 17	Polyps remaining unchanged n = 13	Polyps showing regression[+] n = 5	Total[*] n = 35
1983	2.8mm ± 0.2	3.3 ± 0.2	3.6 ± 0.2	3.1 ± 0.1
1985	4.1mm ± 0.2	2.4 ± 0.2	3.6 ± 0.2	

[+] p = 0.05
[*] p = 0.01

Development of new adenomas

	Adenoma group n = 102			Control group n = 77		
	Males	Females	Total	Males	Females	Total
Old adenomas	25	10	35	0	0	0
New adenomas	7	3	10	0	0	0

194 polyps seen at first endoscopy 143 (74%) recovered
35 adenomas

Recovery of adenomas by colonoscopy percentage and size distribution

Konishi & Morson 1187 adenomas removed

	Total	<5mm	6-10mm	10+mm
Right	8.2	64	18.5	17.5
Transverse	13.6	69.2	17.4	13.4
Descending	18.7	44.6	31.1	24.3
Sigmoid	47.0	22.2	38.8	39.0
Rectum	12.5	48.0	29.0	23.0
TOTAL		**39.3**	**31.6**	**29.1**

O'Brien et al. U.S.A. Gillespie 1979, St. Marks
3371 adenomas from 1867 patients

Caecum	7.6	5.0
Ascending	8.6	6.9
Hepatic flexure	4.6	3.7
Transverse	10.1	16.1
Splenic flexure	4.1	5.8
Descending	13.9	19.2
Sigmoid	43	40.0
Rectum	8.1	3.2

Colorectal carcinoma found by screening and a control population

Hardcastle, Nottingham

	Control	Screened
Right	15	8
Transverse	6	11
Descending	5	1
Sigmond[+]	22	42
Rectum	52	38

[+]increased incidence of sigmoid carcinomas and in a screened population

Distribution of adenomas autopsy studies 2

Percentage adenomas by site

	6	7	8All	8>1cm	8Ca	1Observed vs expected no by length of segment	1 Percentage length of segment	2 Percentage length of segment	3Percentage length of segment
Caecum	7	6	18	26.6	12.9	2.2	3%	2.8	5
Ascending	33.9	27	19	13.3	3.4	1.5	14%	13.1	14
Transverse	28.4	20	25	12	7.7	0.8	34%	35.5	29
Descending	8.8	13	11	10.6	3.7	0.7	20%	16.8	14
Sigmoid	18	19	20	32	18.9	1.0	21%	23.0	24
Rectum	3.9	16	7	5.3	53.4	1.1	8%	8.7	9

6 Chapman 1963 n = 443, New York, U.S.A.
7 Feyter 1931
8 Blatt n = 556, New York, U.S.A

1 Clark *et al*
3 Eide & Stalsberg
3 Rickert

Presence of multiple adenomas and their number by age and sex of patient expressed as a percentage of the total in each age group

Vatn & Stalsberg, Oslo, 1982

Age Male	Cases examined	No adenomas	One adenoma	2-4 adenomas	5-9 adenomas	10+ adenomas
<50	31	73.4	6	10	6	6
50-59	71	61.9	16.9	16.9	1%	2%
60-69	69	49.2	17.3	21.7	10.1	1.4
70-79	49	20.4	24.4	32.6	20.4	2%
80+	44	29.5	29.5	15.9	13.6	11.3
Female						
<50	14	85.8	14.2	-	-	-
50-59	29	65.5	6.8	24.1	2.6	3.4
60-69	31	61.2	22.5	12.9	3.2	-
70-79	51	54.9	23.5	15.6	5.9	-
80+	56	44.6	23.2	21.4	7.1	3.5
TOTAL	**445**	**228**	**87**	**84**	**40**	**14**
Overall frequency		(51%)	(19.5%)	(18%)	(8.5%)	(3.1%)

Polyp follow up

In a radiological retrospective study of 2226 patients with large adenomas > 1mm Stryker et al suggested the cumulative risk of diagnosis of cancer in these patients was 2.5% at 5 years, 8% at 10 years and 24% at 20 years. Hoff et al followed 215 polyps <5mm for 2 years. Seventeen of 35 adenomas enlarged, 13 remained unchanged and 5 reduced in size. Adenomas showing growth increased in size from a mean of 2.8 $\pm$ 0.2mm to 4.1 $\pm$ 0.2mm This data suggesting that small adenomas grow very slowly and may even regress.

Eide compared the adenoma and carcinoma prevalence of Northern Norway and calculated the annual risk of conversion of an adenoma to a carcinoma to be 0.25% for all adenomas, 3% of adenomas > 1cm, 17% for villous adenomas and 37% of those showing severe dysplasia.

IS POLYPECTOMY WORTHWHILE?

Christopher B Williams

St Mark's and St Bartholomew's Hospitals, London

Increasingly flexible endoscopy is the first-line diagnostic methodology in the colorectum (flexible sigmoidoscopy or total colonoscopy). Rigid proctosigmoidoscopy and air-contrast barium enema retain a role as established procedures which are more readily accessible in many hospitals. Larger sessile polyps in the rectum are best managed by the proctologist by local surgical means under general anaesthesia to allow relaxation and good access (whether by conventional excision per rectum or through a stereo-optic operating proctoscope.

Flexible endoscopy is probably 95% accurate for polyps over 5mm in diameter and at least 75% acurate for smaller polyps down to 1-2mm. Naked-eye the endoscopist cannot usually be sure what the histology of a polyp is, and "polypectomy" is effectively used as a way of obtaining a histological speciment - partial during "hot-biopsy" electrocoagulation or complete after snare-loop polypectomy. The procedure is normally on a walk in-walk out basis. Drinking bowel preparation at home, and a mild intravenous sedation if the patient wishes it, are the only measures required before polypectomy.are The relative easy and accuracy of colonoscopic polypectomy are a boon

compared to the previous routine of repeated x-ray surveillance until polyp enlargement indicated abdominal surgery. However the endoscopist's ability to diagnose and treat polyps creates a logistic problem in managing larger numbers of patients because of the obligation of follow-up. There is also the scientific dilemma that, since the smallest polyps are so easily destroyed, the natural history of polyp development and cancer risk cannot ethically be studied without endoscopic intervention, which inevitably destroys the evidence. The past literature on the subject is sketchy and dependent on less accurate methodology including rigid endoscopy and barium enema, only a single study having a control population, but all suggesting 30-40% new polyp formation (and some cancers) over a 5-10 year follow-up period. Stryker, looking back at Mayo Clinic x-rays, calculates the likelihood of a cancer developing at a polyp site (untreated) as 2.5% at 5 years, 8% at 10 years and 24% at 20 years.

First presentation polypectomy

The literature is unequivocal on the value of polypectomy on first presentation. Even removing the non-precancerous juvenile polyps of children saves the child and its parents the anxiety of recurrent bleeding. In hamartomatous polyposis (juvenile or Peutz-Jeghers) the cancer risk is low but significant, and in avoiding bleeding or anaemia polypectomy is highly worthwhile. Of adenomas on first presentation about half are found to be in the "danger" size range of 1cm or greater, and 5% overall already contain invasive carcinoma.

Malignant polyps

Even adenomas with invasive carcinoma or polypoid cancers can be safely removed endoscopically. Subsequent surgery is unnecesary providing that histological findings show that the cancer is not too close to the resection line and is well or moderately-well differentiated - which is generally the case. It is so unusual to find resectable residual cancer at surgery that even doubtfully removed or sessily malignant polyps are now increasingly managed endoscopically in view of the more potential risks of surgery in the elderly patients usually involved. Follow-up of the polypectomy site is easy and accurate if the technique of submucosal India-ink tattooing is used.

Large and sessile polyps

The endoscopist can, with relative safety, remove even quite large sessile polyps piecemeal, and if necessary in several sessions. Many apparently large pedunculated polyps prove actually to be easily snared because the stalk is of lesser diameter, presenting no technical difficulty in removal. The risk of immediate or delayed haemorrhage which previously occurred in around 1% of polypectomies can virtually be prevented by basal or stalk pre-injection with adrenaline or adrenaline-sclerosant mixture. Inevitably with large sessile polyps there is a small risk of bowel wall damage with resulting "post-polypectomy syndrome" of pain and fever (conservatively managed with antibiotics) but frank perforation can occur - usually uneventfully managed with surgery.

Small polyps

Whereas larger polyps carry sufficient risk of symptomatic bleeding or malignancy to justify removal almost without question, the value (other than in histological terms) of destroying small polyps is less certain. The majority may never grow but a few will, some containing severe dysplasia, and their future risk or rate of growth are uncertain on present evidence. The concept of creating a "clean colon" free of adenomas is attractive and reassuring for all concerned, although there is a risk that taking this policy too seriously could result in general hysteria. However if a polyp is a "time-bomb" most patients want maximum protection for themselves, even if the long-term risk seems small to an epidemiologist.

In the recto-sigmoid, especially on limited examination, it is useful to know if small polyps seen are, or are not, adenomas. Although some have said that patients with distal hyperplastic polyps merit colonoscopy because of increased likelihhood of proximal colon adenomas most authors consider that this is not the case. However if multiple (ten or more) hyperplastic polyps are present, especially if some are larger or there are coexisting adenomas, the patient has "metaplastic polyposis" and some cancer risk, and so merits colonoscopy and follow-up.

Technically it is extremely quick and easy to biopsy and destroy polyps up to 5mm in diameter with "hot-biopsy" electrocoaguation, which yields interpretable histology in 95% of cases. Large hot-biopsy series show 50% of small polyps in the rectum and sigmoid colon to be adenomas and 75% of those in the proximal colon. However, hot biopsy has a small complication rate (usually delayed haemorrhage, but a few perforations reported), especially if heat is too-long applied or the technique is used on too large polyps which are more safely snared and aspirated into a polyp "suction trap". The answer for the colonoscopist may be to use the newly developed bipolar electrocoagulating forceps, which localise all heat to the polyp itself with no risk to the bowel wall. The lack of histology after bipolar destruction may be considered unimportant compared to the safety gain, especially in the thin-walled proximal colon.

Follow-up and surveillance?

Cancer patients

After initial presentation colonoscopy to exclude a second cancer or large polyps it has been persuasively argued that over-zealous follow-up is a waste of time in life saving terms, and that resources may be better used to screen other patient groups, such as first degree relatives of cancer patients under 45 years, or those with multiple adenomas.

Adenoma follow-up

Apart from Ekelund's small controlled pre-endoscopic study evidence that follow-up polypectomies prevent cancer is unsubstantiated (even though likely). To prove the matter conclusively would require unrealistic, probably unethical, trials of thousands of patients. The large US National polyp Study, the St. Mark's/CRC adenoma follow-up study and that of Kronborg should yield some guidelines as to which adenoma-bearing patients are at particular risk and justify frequent follow-up (perhaps 2-3 yearly). Others, such as those with only a single small tubular adenoma may need no follow-up at all. In all reports, small adenomas under 1cm diameter account for 84-89% of polyps found at follow-up after initial polypectomy, suggesting that patients previously at high-risk are changed by prior polypectomy and subsequent surveillance to low or normal risk status. 30-40% of follow-up patients have adenomas by 3-5 years and the percentage rises at longer intervals.

Since the object of follow-up is prevention of cancer or cancer surgery (rather than "adenoma-hunting") and colorectal cancer accounts for less than 2% of deaths over 80 years of age there is a strong case for stopping follow-up at 75 years unless the patient insists on it. Hoff points out that even with structured (2-4 yearly) follow-up arrangements there is a tendency to doubling of patient load every eight years and rationalisation is essential.

Genetic risk

Until gene-probes become available colonoscopy (with polypectomy) is the logical screening method for those with two or more relatives with colorectal cancer, especially if the cancer occurred under the age of 40-45 years and in the proximal colon. Although it may be difficult or impossible to prove benefit of prophylactic polypectomy in cancer prevention terms even in affected "high-risk" patients, the peace of mind given them by 3-5 yearly examinations is considerable. By contrast several studies suggest that an aggressive policy for colonoscopy in those with only a single first degree relative with colorectal cancer is not worthwhile.

Does identification of small adenomas indicate colonscopy?

The usefulness of adenomas found on distal screening examinations as a "marker" for increased risk in the proximal colon has been assumed by most clinicians, since at least 30% will have other adenomas proximally. On the other hand others conclude that a small adenoma distally has little significance. Retrospective analysis of long-term clinical follow-up over a mean of 14 years has a large cohort of St. Mark's patients with rectal adenomas removed shows that rectal cancer

incidence is indeed lowered (W. Atkin and B. C. Morson, personal communication, 1990). In this group the overall colonic cancer incidence was double that of the normal population, but the long-term colonic risk of those with only small tubular adenomas was no greater than that of the average population.

Conclusion

The conclusion must be that polypectomy is worthwhile, especially in symptomatic patients or on first presentation. There must however be rationalisation of follow-up or surveillance programmes, which can be logistically overwhelming for relatively small reward.

INTERVENTION STRATEGIES AND THEIR EVALUATION

Professor Nicholas Wald

There are three main intervention strategies that may be applied in reducing mortality from cancer of the colon and rectum, namely dietary change, screening and treatment. They effectively fall under the conventional strategies of primary, secondary and tertiary prevention.

Primary prevention

Diet is the main factor that influences the risk of cancer of the colon and rectum. Other factors, such as the possible effect of smoking on rectal cancer, may play a minor role but are not likely to be a major part of any public health intervention strategy. The difficulty with incorporating dietary modification in any proposed intervention is the lack of knowledge over what specific dietary component is involved. It may be a class of nutrient, such as an excess of fat, or a lack of non-starch polysaccharide, or it may be a specific chemical nutrient such as lack of beta-carotene. In the former case, the only feasible intervention is to change the general diet, whereas in the latter case the possibility of specific supplementation, such as taking beta-carotene capsules, can be considered. In either case the basic evidence for possible efficacy is likely to arise primarily from observational epidemiological studies, supported by plausible biological data and possibly evidence

from experiments in animals. Whether observational data alone can demonstrate a cause and effect relationship is uncertain. It certainly has been able to do so with respect to fat intake and ischaemic heart disease. The clinical trials of dietary and pharmacological intervention designed to reduce serum cholesterol have been of value in determining the reversibility of the risk of ischaemic heart disease and the time span over which a reduction in risk of disease can be demonstrated, rather than being the main source of evidence on whether such dietary changes do themselves result in a benefit. On this issue the observational data have been sufficient, together with human experimental evidence, that diet can reduce serum cholesterol. However, the conclusiveness of the evidence on diet being a cause of ischaemic heart disease has depended on knowledge of the role of serum cholesterol. There was no doubt that serum cholesterol was strongly related to the risk of ischaemic heart disease and that this link was critical in the causal sequence of events. It was also incontrovertible that dietary change could lead to changes in serum cholesterol. It was thus a logical consequence that dietary change could lead to changes in the risk of ischamic heart disease.

The difficulty in the evaluation of evidence on diet and the risk of colon cancer is that we do not have an intermediate 'metabolic' marker of the risk of colorectal cancer, which is known to be etiologically linked to the risk of the disease. If we had, we could study experimentally what dietary changes might alter this metabolic marker. We are only left with the options of examining the effect of general

changes in diet on the risk of the disease itself, an exercise that requires a massive medical and scientific effort involving the study of tens of thousand of individuals in randomised trials with follow-up for many years. In spite of the magnitude of the task such trials are under way. For example, the trial of beta-carotene supplementation in the prevention of cancer among American physicians, and the chemo-prevention trials being carried out in China under the auspices of the US National Cancer Institute. These trials however are testing the supplementation of a specific micro-nutrient taken in the form of specially-prepared capsules. The use of randomised trials of dietary modification in the prevention of cancer in general, or colorectal cancer in particular, is not something that has yet, to my knowledge, been undertaken. The size of such trials in the prevention of cardiovascular disease have been sufficiently daunting; they would have to be many times greater in the prevention of specific cancers. For the present, therefore, we must probably make practical inferences from observational data and act on the basis of a balance of probabilities rather than on the basis of conclusive evidence. This is not to diminish the value of the evidence that may be available. For example, the fact that cancer of the colon is rare in Japan where little fibre is eaten must weaken the notion that fibre is a necessary prophylactic for this disease and increase the likelihood of an important preventive role of another dietary constituent with higher consumption in Japan. Starch is a possibility. The fact that colon cancer is relatively common further shifts the balance of evidence from fibre to starch. The evaluation of results of changes in diet are likely to involve examining changes over time within communities to see whether a particular change in food intake in a country is

reflected in changes in risk. Changes in fat intake have been correlated against changes in ischaemic heart disease mortality in different countries, particularly the United States.

Secondary prevention

The mainstay of the evaluation of methods of screening in the prevention of cancer of the colon and rectum must be, firstly, the demonstration that a screening method can detect early disease and, secondly, the demonstration that this method can, in a randomised clinical trial, reduce age-specific mortality from that disease. The first is relatively easy to demonstrate, for example, that occult blood testing or flexible sigmoidoscopy detects early cancer of the colon. The second is much more difficult, requiring a scale of activity that cannot be achieved by individual centres over short space of time. The magnitude of the problem, however, should not be a reason for rejecting it because there is no satisfactory alternative and the dangers of not evaluating such methods are that they would be introduced 'willy nilly' and become accepted without us ever knowing whether they are effective and, if they are, how large a benefit they confer. In spite of the considerable cost of evaluating such screening methods the costs of not evaluating them are substantially greater, both in medical and financial terms.

Treatment

Treatment (tertiary prevention) is likely to remain the main intervention against colorectal cancer over the next few years until methods of dietary prevention and screening are better understood and applied. Here, as with screening, the mainstay of evaluation is the randomised clinical trial, organised by professional clinical trialists in collaboration with surgeons, oncologists, pathologists and other appropriate specialists, often on a multi-centre basis. The aim must be to obtain clear answers to important therapeutic questions in as direct and expeditious way as possible. In these trials, as indeed with large scale clinical trials in general, simplicity and size must be of the essence, since the expected changes in mortality are likely to be at best moderate (say a reduction in mortality of 20%).

Summary

In the long term dietary intervention has the greatest potential for the prevention of cancer of the colon and rectum. At present, the specific dietary changes required for such prevention have not been identified. Their specification is likely to arise more from deduction and inference based on observational epidemiology backed by basic biological evidence than from human experimental evidence derived from clinical trials - the use of specific micro-nutrients being a notable exception. The evaluation of screening and treatment methods should rest principally on the results from randomised clinical trials.

DIETARY FACTORS AND COLORECTAL CANCER RISK

Peter Boyle and Julian Little
International Agency for Research on Cancer, Lyon

Few specific risk factors of a non-dietary origin have been established for colorectal cancer: inflammatory bowel diseases and familial polyposis syndromes produce a high risk of colorectal cancer in affected individuals but account for only a small proportion of the overall incidence of colorectal cancer. The role of adenomatous polyps is discussed elsewhere in this symposium.

It has been a fairly consistent finding in studies which have examined the issue that energy intake is higher in cases of colorectal cancer than in the comparison group although the mechanism is complex (Willet, 1989). Physically active individuals are likely to consume more energy but recent studies suggest that physical activity reduces colorectal cancer risk (Vena et al., 1987; Slattery et al., 1988). The available data, however, suggest a lack of an association between obesity and colorectal cancer risk (although study of this factor is methodologically complex in colorectal cancer where weight loss may be a sign of the disease). This positive effect of energy does not appear to be merely the result of overeating, therefore, and may reflect differences in metabolic efficiency. If the possibility that the association with energy intake is a methodological artefact is excluded (it seems unlikely that such a consistent finding would emerge from such a variety of study designs in a diversity of population groups which have been studied), it would imply that individuals who utilise energy more efficiently may be at a lower risk of colorectal cancer.

There appears to be consistent evidence from epidemiological studies that intake of dietary fat is positively related to colorectal cancer risk: consistent evidence is obtained from ecological studies, animal experiments, case-control and cohort studies although there have been few methodologically sound analytical studies performed in humans. Many of these studies have failed to demonstrate that the association observed with fat intake is independent of energy intake. The specific fatty acids in the diet may also be important: animal experiments suggest that linoleic acid (an N-6 poly-unsaturated fatty acid) promotes colorectal carcinogenesis (Zaridze, 1983; Sakaguchi et al., 1984) and that a low fat diet rich in eicopentaenoic acid (a N-3 poly-unsaturated fatty acid) has an inhibitory effect on colon cancer (Minoura et al., 1988). However, there have been no epidemiological studies conducted to date regarding N-3 and N-6 fatty acids and colorectal cancer risk.

The original hypothesis of the protective effect of dietary fibre was based on astute observation and a hypothesised mechanism whereby increasing intake of dietary fibre increases faecal bulk and reduces transit time (Burkitt, 1971): more recent thinking suggests that this mechanism may not be as relevant as previously thought (Kritchevsky, 1986). The term "fibre" encompasses many components each of which has specific physiological functions. The commonest classification is into the insoluble, non-degradable constituents (mainly present in cereal fibre) and into soluble, degradable constituents like pectin and plant gums which are mainly present in fruits and vegetables. Epidemiological studies have reported

differences in the effect of these components. For example, Tuyns et al. (1987) and Kune et al. (1987) found a protective effect for total dietary fibre intake in case-control studies and the same was found in one prospective study (Heilbrun et al., 1989). However, a larger number of studies could find not such protective effect (see Willet (1989) for review). The large majority of studies in humans have found no protective effect of fibre from cereals but have found a protective effect of fibre from fruit and vegetable sources (see Willet, 1989). This could conceivably reflect an association with other components of fruits and vegetables, with "fibre" intake acting merely as an indicator of consumption.

Although calcium has been proposed as potentially having a modifying role in colorectal carcinogenesis (Newmark et al, 1984) little supporting evidence is forthcoming from epidemiological studies (Sorenson et al., 1988). These studies in humans are of limited value because of questionable study design or the inadequacy of the estimation of diet. A number of studies have reported positive associations with alcohol consumption but it remains to be proven whether the putative association is with alcohol per se and not with the calorie contribution of alcohol. There is some experimental evidence that vitamin E and selenium may be protective against colon tumours (Zaridze, 1983) and there is support for the hypothesis that vitamin A and/or its precursor beta-carotene protects also (Willet, 1989). Lactobacilli, found in some dairy products, may have a favourable effect on the intestine (Goldin and Gorbach, 1984). Twelve case-control studies of sufficient quality have addressed the issue of coffee consumption and the risk of colorectal cancer and 11 of these have indicated negative (protective) associations. No

association has been found with tea drinking or caffeine from all sources.

In summary, dietary factors are most probably the important determinants of colorectal cancer risk. Methodological problems in nutritional epidemiology prevent an unequivocal interpretation of the available data. Our interpretation is that an effect of saturated fat appears to exist independently of energy intake and that vegetable fibre, directly or indirectly, appears to be protective, as does coffee consumption. Meat intake may also increase risk but whether this is independent of its fat content or its contribution to calories is currently unclear: if independent, the risk could be related to mutagenic products formed in the cooking process. Associations with other dietary factors, including cereal fibre consumption, remain open questions.

DIETARY FAT AND COLORECTAL CANCER

Michael Hill, Porton Down, Salisbury, Wilts

There have been many ecological studies of diet and colorectal cancer, almost all of which have shown a very strong relationship between the risk of the disease and the amount of dietary fat, particularly animal fat. Although some case-control studies have shown fat as a risk factor for colorectal cancer, the relationship has always been weak and to some unconvincing. In general, case-control studies rather than ecological studies usually provide the stronger evidence for causation. Unfortunately in the case of diet this will only be true when better instruments are developed for measuring dietary intake overtime in individuals and when the types of controls are easily identified. Case-control studies of diet and colorectal cancer have failed to show strong relationships with any dietary item. This is, in part, due to the fact that dietary recall methods are relied on to determine the diet in the years prior to the disease becoming symptomatic. Such methods are notoriously inaccurate because they rely on memory. Further, colorectal carcinogenesis is a multistage process in which the causes of the individual stages clearly differ. This makes the choice of controls when studying the overall process very difficult. The failure of case-control studies to offer strong support for a role for any dietary item in colorectal carcinogenesis is, therefore, hardly surprising.

A good animal model of the disease could help to clarify the role of diet. Unfortunately the existing animal models, whilst being useful for the study of cell biology or treatment of malignancies, are not helpful to those studying etiology. Thus, whereas animal studies apparently offer strong support for a role for dietary fat in the promotion of colorectal cancers, the results have little application to humans.

The postulated role of dietary fat could be made more plausible if a convincing mechanism could be proposed. From our studies of the role of bile acids, the results indicate that bile acids are important in the progression from adenoma to carcinoma (but have no role in adenoma formation). The faecal bile acid composition and concentration depends on diet and supports a role for both fat (causal) and some fibre components (protective). The prevalence of adenomas in western populations is very high, suggesting that the agents responsible for their causation are ubiquitous and likely to be difficult to counter. The prospects for prevention of colorectal cancer are therefore most favourable at the promotion stage - the progression from adenoma to carcinoma. Thus the role of dietary fat, if it is at this latter stage of the disease is not significant.

In summary, there is evidence of a role for dietary fat in the causation of colorectal cancer. This role appears to be indirect (via the bile acids) and is at the promotion stage rather than at initiation of carcinogenesis.

STARCH AND FIBRE IN PREVENTION OF COLORECTAL CANCER

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The suggestion that dietary fibre is protective against cancer of the large bowel was made 20-30 years ago. The suggestion was based on the rarity of bowel disorders, including cancer, in the rural African compared with people living in Western countries. These differences in cancer incidence were attributed to the presence of "fibre" in the rural African diet. Subsequent studies using accurate methods of fibre analysis such as non-starch polysaccharides (NSP) have not confirmed a higher intake of NSP in low-risk populations, eg the Japanese, although rates of colorectal cancer in this population are fast increasing with westernization. Correlation studies within Britain and Scandinavia, populations at higher risk and consuming elevated amounts of meat and fat, suggest that there is a protective association between cancer occurrence and NSP intake. Stool weight is inversely related to colorectal cancer incidence.

In animal models, NSP, fed in the form of bran, reduces the number of tumours induced by chemical carcinogens, and cellulose may have a similar effect. The faeces of some individuals contain mutagens, and faecal mutagenicity can be reduced by supplements of bran. The mutagens involved have not been isolated, although fecapentaenes and heterocyclic amines are possible candidates.

Extensive studies in humans have shown that NSP has marked effects on colonic function and bacterial metabolism. On reaching the large gut, NSP acts as an energy substrate for the colonic flora,

stimulating fermentation with a net increase in faecal weight, bacterial mass, short chain fatty acid and gas production. The large intestinal contents are diluted and transit time shortened. Recent observations have shown that substantial amounts of starch survive digestion in the small bowel and are available also for fermentation in the large gut. Short chain fatty acids are trophic factors for the colonic mucosa and starch appears to be beneficial as a substrate for fermentation because yields of the short chain fatty acid butyrate are increased both in vitro and in vivo. Butyrate is an energy substrate for the colonic mucosa and an antiproliferative and differentiating agent in cell culture lines. Possible mechanisms whereby starch and non-starch polysaccharides may protect against colorectal cancer therefore exist.

The majority of individual case-control epidemiological studies suggest that fibre-containing foods are protective in colorectal cancer, although this effect is largely due to vegetable, rather than cereal, consumption. The association with vegetables may be due to the fact that they are the major source of NSP in Western diets, or that they contain micronutrients and pharmacologically active substances for which a general protective role in cancer has been described. Case control studies are difficult to evaluate particularly in large bowel cancer where bowel habit and diet may be prone to changes in response to symptoms. There are a number of planned prospective studies in Europe in which intakes of starch, vegetables and NSP will be measured.

Intervention trials with bran in patients with polyps at greater risk of cancer are also in progress. So far, one recent intervention in a small number of patients with familial adenomatous polyposis suggests that NSP, rather than Vitamin C and E, appear to inhibit the number of adenomas appearing in the rectal stump following colectomy.

Insufficient evidence is presently available for a definitive assessment of the protective effect of NSP in colorectal cancer, and the effect of starch has not been tested epidemiologically. Future research should concentrate on the prospective and intervention approach in order that dietary measures can be linked to biomonitoring of intestinal risk factors and eventually specific genotoxic events. Techniques suitable for such procedures in humans are currently being developed. At present, there are good reasons on other health grounds for suggesting an increase in the NSP and starch content of the average UK diet and no evidence that such an increase would augment colorectal cancer risk.

PRINCIPLES AND APPROACHES TO SCREENING

Dr Howard Cuckle, St Bartholomew's Medical College

Screening is the identification among apparently healthy individuals of those who are at sufficient risk of a particular disease to justify performing diagnostic tests which are too expensive or hazardous to be offered more widely. In cancer screening the aim is either (i) to diagnose the disease at a stage that is more amenable to treatment (eg breast cancer) or (ii) to diagnose pre-malignant changes that when treated would prevent the disease occurring (eg cervix cancer). In order to explain the principles of cancer screening I will assume the former aim but the conclusion will apply to both.

If we assume that there are no practical or financial restraints and that the tests and subsequent treatment are acceptable the central question of cancer screening becomes whether early treatment is efficacious. To establish this it is not sufficient to simply show that the best treatment for early stage cancers is being used, rather it must be shown that treatment at an early stage per se is better than treatment at a later stage. It is a commonly held belief that this is easy to demonstrate for diseases like cancer where the survival rate can vary widely with the stage of diagnosis. The argument here is fallacious. For example, in lung cancer there is a strong negative correlation between stage and survival, but although large studies have found that chest X-rays and/or sputum sampling leads to earlier diagnosis they have had no effect on the mortality rate. This apparent paradox is explained by statistical bias.

The first and most obvious bias is called the "lead time" bias. Suppose that a cancer was diagnosed incidentally whilst investigating some completely unrelated problem, and the patient refused treatment. The time from diagnosis to death would necessarily be longer than had the cancer been diagnosed clinically when the patient would have presented with symptoms, yet the date of death would have been unchanged. Thus, the extra time the cancer was observed (the "lead time") increased the survival time but did not change the outcome. The second bias is called the "length" bias. This arises because of the variability in severity of disease, so that for example some cancers are aggressive and will lead to death just a few years after initiation whereas other cancers of the same site are indolent and may take decades. Since the latter spend more time in the preclinical but screen detectible stages there are more opportunities for incidental diagnosis. It follows that in a group of cancers diagnosed early there will be a disproportionate number of indolent cases with good survival.

As a consequence of these biases in order to evaluate early treatment the mortality rate and not the survival rate has to be used, comparing it in those who are treated early and in similar individuals who are not. This is unlikely to be possible directly. Once an early diagnosis is made through screening, unless the treatment is unacceptably radical, it would be unethical to perform a randomised clinical trial in which say half are treated immediately and half only when there are symptoms. However almost the same effect can be achieved indirectly by performing a randomised trial of screening

itself by identifying a target population and allocating half to be offered screening and the remainder as controls. Those in the screening arm will tend to have an early diagnosis and those in the control arm will present clinically at a later stage. When screening first becomes technically possible it will be a rare resource which cannot be offered to all and so taken together with the lack of proven efficacy it is ethical to allocate the offer of screening at random. Indeed, it could be argued that it would be unethical to do otherwise.

Randomised trials of cancer screening with mortality as the endpoint need to last for many years and so it is natural to examine other features which may provide an earlier indication of possible success of the trial. Such indicators include a) the incidence rate of advanced cancer in the two arms b) the incidence rate of cancer in the interval between screening rounds c) the stage distribution of cancers diagnosed at screening and d) performance characteristics of the test itself such as the extent it separates affected from unaffected individuals and the risk of having the disorder given a screen positive result. All of them are subject to lead-time and length bias but they do at least provide negative information. For example if the proportion of early stage disease among cancers diagnosed at screening is not much more than that in the control arm then success is unlikely. The earliest indicator is usually the test performance. The extent of separation it provides can be quantified by the detection rate (DR) (proportion of affected with positive results) and the false positive rate (FPR) proportion of unaffecteds with positive results). Sometimes the terms sensitivity and specificity are used: they are numerically equivalent to the DR and 100% minus FPR respectively. If the test is a continuous variable or can take on a range of values the DR and FPR will be determined by the cut-off level

chosen. The risk of being affected among screen positives expressed as a percentage is known as the positive predictive value (PPV). The risk is dependent on the DR and FPR as well as the prevalence of the disease in those being screened. Thus the PPV of a test can differ in two studies if one chooses a more extreme cut-off level (so that the ratio of affected to unaffecteds is more favourable) though this will be at the expense of detection.

The PPV's could also differ if the same cut-off level were used but one study applied the test in a population with a higher prevalence.

When screening for cancer these performance characteristics are impossible to derive directly because there is no independent determinant of who is affected at the time of test. This is not such a problem for the FPR which can usually be approximated by the total positive rate (proportion of all tested who are positive). One way of estimating the DR is to define affected cases as those found at screening or surfacing clinically in the screen negatives within a specified period. There are two problems with this. Firstly, those detected at screening, particularly in the first or "prevalent" round will include some who may never have surfaced clinically (ie over-diagnosis). Secondly, the follow-up period is arbitrary. Those who surface soon after screening are likely to have missed by the test but missed cases may surface many years later.

Because screening is carried out among apparently healthy individuals as a public health measure it is subject to a greater burden of proof than tests carried out in normal medical practise. When a patient seeks the help of a doctor, say following the onset of symptoms, tests may be done which have little or no proven benefit but which, to the

best of available knowledge, are worthwhile. In screening the roles are reversed as it is the doctors who seek out patients to have tests. That is why there is a need to have rigorous evaluation before the introduction of the tests. This evaluation is particularly difficult in cancer screening.

MOLECULAR GENETICS AND COLORECTAL CANCER SUSCEPTIBILITY

By M G Dunlop MBChB, FRCS(Ed)

Although dietary factors are clearly implicated in the aetiology of large bowel malignancy, there is substantial evidence to suggest that genetic susceptibility interacts with environmental factors to influence colorectal cancer (CRC) risk. Such genetic effect is in addition to the syndrome of Familial Adenomatous Polyposis (FAP) in which affected individuals have a cancer risk approaching 100%. Many studies (Bonelli 1988, Burt 1985, Duncan 1982, Lovett 1976, Macklin 1960, Woolf 1958) have shown familial clustering of benign and malignant colorectal neoplasms which is not restricted to the syndrome of hereditary non-polyposis CRC as described by Lynch (Lynch 1985i). Such familial aggregation cannot be accounted for by the simple hypothesis of common exposure to high levels of environmental carcinogens since the incidence in spouses of affected patients is that of the general population (Cannon-Albright 1988, Jensen 1980). The data support the existence of a gene defect resulting in colorectal adenomas and carcinomas with a population frequency of 19% and transmitted in a Mendelian dominant mode (Cannon-Albright 1988). If confirmed, this has resounding implications for screening and early detection of premalignant and malignant colorectal neoplasms.

The molecular genetics of CRC are also now becoming more fully understood. Following the mapping of the gene for FAP (apc) to chromosome 5q21-22 (Bodmer 1987), specific and consistent deletions of that gene in CRC tissue have been demonstrated (Ashton-Rickardt 1989, Solomon 1987). This suggests that apc has tumour suppressor

gene activity and implicates loss of apc in colorectal carcinogenesis. However, there is also the possibility that a class of apc mutations could be inherited. There is now clinical and molecular genetic evidence to support this notion. Mandibular osteomas (a feature of FAP) occur with undue frequency in apparently sporadic cases of CRC (Sondergaard 1985) and in one large kindred genetic linkage has been established to a disease gene resulting in variable numbers of adenomatous colorectal polyps using chromosome 5q DNA markers (Leppert 1990). This suggests that apc mutations may indeed confer an increased risk of CRC to a much greater extent than that limited to the classical syndrome of FAP.

Aberrations at other genetic loci are also known to be involved in the biology of CRC. Since the disease is clinically quite heterogeneous there is reason to suspect that genetic heterogeneity may also be operant and that any one of these loci could be involved in CRC susceptibility. Recently a large gene on chromosome 18q has been identified which is altered in CRC tissue in a very high proportion of cases (Fearon 1990). Notably, in 1985 genetic linkage of heritable non-polyposis CRC was established to the Kidd blood group (thought to be on chromosome 2 at that time) in one large kindred (Lynch 1985ii). Kidd blood group has been recently reassigned to chromosome 18q (Boman 1988) and, very recently, a DNA marker for the new DCC gene has been shown to map very close to Kidd (B Bogelstein personal communication). The race is now on to show genetic linkage of the DCC markers to the CRC phenotype in one or more kindreds, though the task may be difficult as not all families will show linkage of 18q.

The involvement of any particular tumour suppressor locus in colorectal carcinogenesis implies inactivation of both copies of such a gene which therefore acts in a recessive fashion at a cellular level. Hence, inheritance of one inactivating mutation would increase the risk of a second, somatic, event having an effect and conferring growth advantage on the altered cell in the colorectal mucosa. We know that multiple genetic aberrations can be detected in CRC tissue (Baker 1989, Vogelstein 1988) and thus any one of these genetic lesions could be involved in the inheritance of CRC (although it is unlikely that activating mutations in oncogenes would be inherited). Two mutational events would be required at one tumour suppressor gene which could be a rate-limiting step (Knudson 1989) and so a two-mutation and multi-step theory of colorectal carcinogenesis are not mutually exclusive. The important genetic abnormalities implicated in colorectal cancer in addition to apc and DCC mutations include inactivating mutations of the gene for p53 (Baker 1989) and also possibly oncogenic p53 mutations (Baker 1989, Iggo 1990) and K-ras mutations (Vogelstein 1988). However other tumour suppressor loci could be involved and might be indicated by a high frequency of loss of genetic material from specific loci scattered about the genome (Vogelstein 1989). Clearly not all individuals with a gene defect predisposing to CRC will develop the disease since inheritance of that mutant gene only confers susceptibility to colorectal neoplasia. Hence the importance of the interaction of genetic with environmental risk factors must be stressed.

Assuming that mutations in a number of colorectal cancer genes are shown to confer a heritable predisposition to colorectal cancer and that these genes and mutations are fully characterised, it is conceivable that mass unselected population screening would be possible and gene carriers identified for intensive screening programs. This is clearly in the distant future and will stimulate ethical debate but screening for FAP using linked DNA markers is already a reality and is influencing patient management. Within the foreseeable future the apc gene will be cloned and it will be possible to screen all individuals at risk of FAP (incidence of FAP is 1/10,000, therefore estimate of those at-risk 1/5000 or around 6000 individuals under 30 years of age requiring screening initially and 200 annually thereafter). The search for heritable apc mutations in non-FAP CRC will then be of great importance.

The life risk of CRC is around 1/50 for the whole of the UK population but if 2 first degree relatives are affected that risk rises to 1/6 (J Slack personal communication). The actual numbers of individuals in the UK falling into this category is difficult to assess but a frequency of hereditary non-polyposis CRC of around 5% of all cases of CRC has been demonstrated (Mecklin 1987). However there appear to be no analyses in the literature which only examine individuals with CRC who actually have sufficient 1st degree relatives to confidently exclude (or confirm) the hereditary nature of the disease in the family.

Thus all the published data will underestimate the actual population frequency of CRC with a strong heritable input. Notwithstanding this, if it is assumed that 1250 cases of colorectal cancer in the UK presenting each year arise in patients with two affected 1st degree relatives and that the gene is inherited as an automsomal dominant then at least 12,500 at-risk individuals in this category alone would require screening if the penetrance is 20% and 2800 individuals if the penetrance is 90%.

Molecular genetic screening would require a search for specific gene mutations since genetic heterogeneity would make linkage analysis impractical. Therefore such screening could be offered to the entire population in view of the findings of Cannon-Albright which suggest a gene carrier rate of 19% (Cannon-Albright 1989).

For the present DNA markers of colorectal cancer susceptibility remain conjectural but research in the field is at an exciting stage and promises much for the future.

SCREENING HIGH RISK GROUPS

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Family studies in colorectal cancer have demonstrated an increased risk in the first degree relatives of patients with colorectal cancer of 2 to 4 times the population risk, (Woolfe 1958, Macklin 1960, Lovett 1976, Anderson 1974) and to a similar extent in relatives of patients with adenomas (Ascari 1986). In addition various dominantly inherited forms of colorectal cancer are now recognised. The best known of these, and that in which there appears to be the highest risk of adenocarcinoma of the bowel, is Familial Adenomatous Polyposis (APC) (Bussey 1975). In addition there are two other dominant conditions with a high risk of colorectal malignancy, Cancer Family Syndrome (Warthin 1913) and Site Specific Colon Cancer (Woolfe 1955). Neither of these latter two conditions are associated with polyposis of the bowel but low numbers of adenomas do occur. Individuals can be assumed to be a member of one of these families if they had three first degree relatives with colorectal cancer or three degree relatives with colorectal cancer and the other commonly occurring adenocarcinomas in CFS. Having calculated risks for individuals it is possible to provide advice and screening. Family history can successively be used as a method of assessing an individual's risk. Invasive screening can be targetted at those at highest risk and produces a high yield of positive examinations.

SCREENING FOR COLORECTAL NEOPLASIA

By Professor J D Hardcastle

Colorectal cancer is a common problem and in many developed countries is the second commonest cause of death from malignant disease. In England and Wales in 1984, 19,240 persons died of the condition. With a disease as common as colorectal cancer an intervention which produces only a small percentage improvement in survival can result in a very significant number of lives saved.

Colorectal cancer becomes symptomatic relatively late in its natural history, often when the tumour has spread beyond the confines of the bowel wall into adjacent tissues, and at times into lymph nodes and distal organs.

Survival following resection is directly related to the degree of spread at the time of surgical treatment, those patients with tumours limited to the bowel wall having an excellent prognosis. The concept of early diagnosis of colorectal cancer evolved as a result of the development of simple faecal occult blood screening tests and the development of colonoscopy.

Screening is likely to influence survival in two ways. Firstly by the detection of tumours early in their natural history when still limited to the bowel wall and amenable to surgical treatment. Secondly by the detection and removal of pre-malignant adenomas, with a resulting decrease in the future incidence of colorectal cancer.

The effectiveness of a screening programme is difficult to determine because of a number of biases that influence these results. More favourable, slowly growing tumours are more likely to be detected by regularly undertaken screening tests (length bias), cancers may be detected earlier in their natural history without any real increase in survival (lead time bias) and individuals who accept an invitation for screening may have intrinsically better survival rates than less health conscious individuals (selection bias). Early outcome measures such as favourable cancer stage and increased detection rate are important indicators of possible benefit but cannot be used as a final determinant of validity.

Faecal Occult Blood Screening Tests

Two main types of test are available: chemical tests based on the guaiac reagent and immunochemical tests. The chemical basis of the guaiac test is the detection of the pseudoperoxidase activity of haem, either as intact haemoglobin or free haemin. The pseudoperoxidase activity of haem catalyses the oxidasation of guaiac reagent by hydrogen peroxide which is a developer solution resulting in a simple colour change. Because of the uneven distribution of blood in the stool two samples are taken from each of three successive stools. Various guaiac tests are available with different levels of sensitivity for haemoglobin in the stool. The most commonly used and evaluated test, the Hemoccult test, produces a positive result when between 2 and 3 mg of haemoglobin is present in the stool. In controlled trials of faecal occult blood screening the performance of the test is satisfactory with low positivity rates and high predictive values of positive tests for neoplasia (Table 1).

Immunochemical tests utilise antibodies directed against intact globin moiety of human haemoglobin and have the advantage of a low sensitivity for upper GI bleeding. As yet there is only limited information available about the performance of immunochemical tests in screening programmes.

Population Screening by Hemoccult Testing

Many uncontrolled screening studies have shown that tumours detected by faecal occult blood screening are at a less advanced pathological stage compared with tumours occurring in symptomatic individuals.

In the Federal Republic of Germany population screening for colorectal cancer was introduced in 1977 using Hemoccult and rectal digital examination. Compliance has been disappointingly low. Analysis of the results is difficult because of incomplete reporting. Adenomas have not been registered in the programme. A Case Control Study has now been set up in an attempt to determine whether mortality from colorectal cancer has been reduced.

The true benefit from screening can best be assessed by performing a prospective randomised controlled trial in which the mortality and morbidity of a group offered screening is compared to a similar group randomly selected from the same population. Four European population studies and a trial involving 30,000 volunteers in Minnesota are at present in progress (Table 1). A second controlled trial in New York, USA has been completed in which individuals were assigned to screening with Hemoccult and sigmoidoscopy or sigmoidoscopy alone. Data from two of the

largest European trials, Nottingham and Funen, are shown in Table 2. In both trials 51% of screen detected cancers are Dukes' Stage A compared with 9.12% in the control group. At the time of surgery, distal metastases are found in 3.5% - 5.7% of the screen-detected cancers compared with over 20% in the control group.

Other prognostic factors also are found to be more favourable in the screen detected cancers. In particular, between 16-23.7% of cancers were removed colonoscopically compared with 0-0.5% in the control group. The effectiveness of screening must however, be evaluated by comparing the whole of the test group, including the non-responders, with the control group. This comparison is shown in Table 3. A significant increase in the number of Stage A cancers is found in the test group compared with the control group, but there are similar numbers of late stage disease in both groups. This is to be expected at this stage in the trials and it remains to be seen if the expected better prognosis of these lesions will result in an overall mortality advantage.

It is unlikely that reliable mortality data will be reported from the European or Minnesota trials before 1994/95. The increased detection and removal of adenomas in the test group compared with the control group gives hope that futures incidence of carcinoma may be reduced by screening (Table 4).

TABLE 1
CONTROLLED TRIALS OF HAEMOCCULT IN SCREENING FOR COLORECTAL CANCER

	Cohort Size	Positivity Rate(%)	Predictive Value(%) (Adenomas & Cancer)
Goteborg Sweden	27,000	1.9	22
Nottingham England	150,000	2.1	53
New York USA	22,000	1.7	30
Minnesota USA	48,000	2.4	31
Odense Denmark	62,000	1.0	58
Burgundy France	47,150	2.1	44

TABLE 2
COMPARISON OF CANCERS DETECTED IN NOTTINGHAM AND FUNEN CONTROL TRIALS

NOTTINGHAM TRIAL

	Screen detected cancers n=122	Control Group cancers n=261
% Stage A	51%	12%
% Liver metastases	5.7%	21.8%
% Colonoscopic polypectomy	23.7%	1.65

FUNEN TRIAL

	Screen detected cancers n=57	Control Group cancers n=166
% Stage A	51%	9.0%
% Liver metastases	3.5%	23.5%
% Colonoscopic polypectomy	16%	0%

TABLE 3

NOTTINGHAM AND FUNEN RANDOMISED CONTROL TRIALS OF FAECAL OCCULT BLOOD POPULATION SCREENING

Stage of Cancers in Test and Control Groups

NOTTINGHAM

Cancer Stage	Test Group offered screening (71,277)	Control Group (71,413)
A	98 (29.4%)	33 (12.6%)
B	94	88
C	73	77
D	66	57
USA	3	6
TOTAL	334	261

FUNEN

Cancer Stage	Test Group offered screening (30,970)	Control Group (30,968)
A	52 (27.3%)	15 (9.0%)
B	57	57
C	32	46
D	40	39
USA	9	9
TOTAL	190	166

TABLE 4

NOTTINGHAM AND FUNEN RANDOMISED CONTROL TRIALS OF FAECAL OCCULT POPULATION SCREENING

Distribution of adenomas according to size in Test and Control Groups

	TEST GROUP		CONTROL GROUP
	Screen Detected	Total	
(Number of persons by largest adenoma)			
NOTTINGHAM		71,277 pers	71,413 pers
< 10mm	67	101	38
10-19mm	201	243	53
> 20mm	115	139(2.0/1000 persons)	39(0.5/1000 persons)
TOTAL	383	483(6.7/1000 persons)	130(1.8/1000 persons)
FUNEN		30,970 pers	30,968 pers
< 10mm	33	65	47
10-19mm	91	113	36
> 20mm	38	54(1.7/1000 persons)	26(0.8/1000 persons)
TOTAL	162	232(7.5/1000 persons)	109(3.5/1000 persons)

FAECAL OCCULT-BLOOD TESTS: THE RISKS AND COSTS

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We live in a post-curative era. Attending the sick is seen as a time-consuming distraction from the real task - the prevention of disease. While the queues of patients lengthen, more time and money is being diverted towards attending the worried well.

Cancer screening is not prevention but early detection; this is believed to "save lives". However, despite efforts devoted to early diagnosis, cancer mortality has not changed during the past 50 years. Cervical screening has proved to be a failure.2 Breast cancer screening does not work. Cancer screening has an almost unlimited potential for metastatic growth: so far screening has been advocated for cancers of breast, lung, bowel, stomach, endometrium, ovary, cervix, testis, penis, bladder, prostate, thyroid, skin, oral cavity, liver, and pancreas. The list is not exhaustive.

In the case of screening for colorectal cancer by occult-blood testing, there are no data to suggest that this method of screening reduces mortality from the disease. Despite the lack of evidence, screening for colorectal cancer has vigorous advocates. "The advocates of screening, usually for impeccable motives, conclude that the pre-existing evidence plus commonsense, in face of the ongoing toll of disability and untimely death, demand mass screening programmes.

In "keeping the faith", screening advocates may find themselves forced to accept or reject evidence not so much on the basis of its scientific merit as on the extent to which it supports or rejects the stand that screening is good."

For example, in the authoritative report by a committee of British experts it was stated that "the interim results from the randomised trials showing that a high proportion of screen-detected tumours are at stage A demonstrates the value of faecal-occult-blood screening." This is an elementary blunder in epidemiological reasoning, as nothing of the kind is "demonstrated" by such observations.

Cancers detected by screening have a better prognosis because of the length bias (ie, slowly growing tumours are more likely to be picked up by screening) and because of the lead-time bias (patients live longer because the disease was diagnosed earlier, even though the time of death is not postponed). A definitive answer about the value of screening can only be obtained from properly conducted randomised controlled trials. The use of randomised controls trials means that a comparison can be made between all the cancers arising in the control group and all cancers, including screen-detected and interval cancers, occurring in the screened group. None of the three such trials published so far has shown any survival advantage in the screened group, (Table 1).

Occult-blood testing is unsuitable for screening, because it does not detect cancer but blood which can come from any source (haemorrhoids, diet interfering with the test, aspirin-induced bleeding, polyps without malignant potential, etc).

The detection and surgical removal of polyps creates additional confusion, as the purpose of screening is to reduce mortality from cancer and not to increase unnecessary surgical operations. Since only about 5% of adenomatous polyps are likely to metamorphose into clinically significant cancer in the lifetime of the screened person, 19 out of 20 such subjects may be treated unnecessarily. It is estimated that 40% of people over the age of 60 have polyps and thus the potential for overdiagnosis and overtreatment is vast. The current polypmania is a surrogate-outcome fallacy. Despite the fact that nearly 50% of the over-50 population in the USA is being screened according to the American Cancer Society guidelines, and millions of polyps have been removed in the process there is no evidence that the mortality from colorectal cancer has been affected.

With an average sensitivity and specificity of the Haemoccult test of 50% and 97% respectively, the application of the test for mass screening would produce about 3000 false positives per 100,000 screened persons, and miss 100 cancers (Table 2).

The harms of occult-blood screening include false alarms to 1-3% of the screened at each round (this problem is cumulative!) with the accompanying anxiety, fear and unnecessary further investigations, operations and iatrogenic harm. In some patients a cancer might be discovered which would not manifest itself within their lifetime, and in other patients, extra cancer years would be added without prolonging their life. (Table 3). Costs to society would include the diversion (waste) of resources from other, more cost-effective uses, and a contribution to national cancerophobia.

TABLE 1

	FUNEN(1)	GOTEBORG(2)	NOTTINGHAM(3)
age group	45-74	60-64	50-74
accepted screening	20,000(67%)	9,000(66%)	28,000(53%)
positive Haemoccult	1%	1.9% 5.8% (hydr)	2.3%
colorectal cancer in screened	37	4 12 (hydr)	63
in nonrespondents and interval cancers	33	26	111
positive predictive value of + Haemocult	17%	5%	10%
False negative rate (interval cancers)	>20%	>78% >14% (hydr)	>26%
Excess cancers (screened vs controls)	84%	120%	50%
Excess adenomas (screened vs controls)	130%	200%	470%
Deaths from colorectal cancer STUDY	7	?	35
CONTROL	5	?	32 (4)
Exclusions of known cases of colorectal cancer STUDY	167 (+ 18 deaths)	?	?
CONTROL	161 (+ 19 deaths)		

1 Kronberg et al, Scand J Gastroenterol 1987; 22: 677-686
2 Kewenter et al, Cancer 1986; 62: 645-651
3 Hardcastle et al, Lancet 1989; i: 1160-1164
4 Chamberlain J et al. Presented at a meeting of the Society for Social Medicine, Dublin, 1987.

TABLE 2

Haemoccult test

average sensitivity	50%
average specificity	97% (1)

Prevalence of colorectal cancer in over 50:

200/100,000

TEST	pos	cancer	no cancer	
		100	2994	PPV = 3%
	neg			
		100	96806	NPV = 99.9% (no test 99.8%)

1 Kobberling J, Windeler J. Der Test auf okkultes Blut im Stulh. Stuttgart, Thieme, 1985.

MASS OCCULT-BLOOD SCREENING

Cost to the screened

1 False alarm to 1-3% of the screened
to 90-97% of the positives

2 Unnecessary intervention
1-3% - sigmoidoscopy
barium enema
colonoscopy
polypectomy

19/20 polypectomies unnecessary

colonoscopy perforation 1/100-1/250

3 Adding extra cancer years

4 False reassurance (50% false negative)

5 Economic costs (medical fees, insurance premiums, time lost from work, travel)

References:

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Exploitation of the fear of cancer by private clinics has become widespread. According to the March 1989 issue of Vogue, the London Bridge Hospital launched a screening service for healthy people, which includes colonscopy at £120 a head. Yet, in the Nottingham trial, there were more deaths in the screened group than in the control. Until it is known whether screening can reduce mortality, it is meaningless to calculate cost-benefit.

At present, screening of healthy people takes place in an ethical vacuum: the screeners have no obligation to inform those invited for screening about the uncertainty of the benefit nor the possible nature and extent of the harm. As the risks of occult-blood screening are likely to outweigh the benefits in any age group,it is imperative that the same protection is introduced for those who are to be screened as already exists for volunteers in clinical trials. "Without conclusive evidence that screening can alter the natural history of disease in a substantial proportion of those screened, screening should not be advertised. Irrespective of feasibility or cost, the public should be informed about the harm-benefit ratio of occult blood screening before being invited to participate."

THE ECONOMIC EVALUATION OF SCREENING FOR COLORECTAL CANCER

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1. Cost and benefits of a screening programme.

Prior to the present study, the economic evaluation of mass population screening for colorectal cancer using data from a randomised controlled trial has never been undertaken. The overall aim of evaluation is to identify , measure and value the costs and benefits of screening an asymptomatic population with faecal occult blood tests . This paper sets out the costs and yield of a screening programme within the framework of a model but drawing on data from the Nottingham study.

Following the Nottingham protocol the screening proceedure to be modelled is as follows:

i) the group to be offered screening is identified from population registers.

ii) tests are posted to the target population.

iii) completed tests are returned to the hospital laboratory, where they are developed.

iv) persons with positive tests are invited to a clinic where they are offered an appropriate diagnostic investigation.

v) appropriate treatment is offered.

Patient costs have not yet been included in the calculations, although they are discussed below.

2. Cost and yield of a screening programme

Trial data on costs and test performance have been derived and are used below in a model of screening using a population representing a typical Family Practitioner committee (approximately 300000 people). The Nottingham study offers screening to people aged 50 to 74. In the F.P.C. area 75000 people fall within these limits and hence are offered the three day Haemoccult test every two years ; this constitutes one screening round.

The parameters used for three day testing are based on current 'best' practice in Nottingham rather than trial averages. After taking into account time trends in the data , compliance with three day testing was 58% with a positive rate of 1.3%. At present there is no proven benefit to earlier detection , hence the yield in terms of cancer and adenomas has been used as an intermediate outcome measure. On investigation 2.3 cancers and 7.47 adenomas have been detected per 10000 acceptors (or about one cancer and six adenomas per ten positives).

Cost parameters are based on observation of practice in Nottingham adjusted to exclude factors relating specifically to clinical research. A three day Haemoccult test costs £1.13 although the costs of postage and development increases this to £1.62. The costs of diagnostic investigations are not routinely available and are therefore based on observations of colonoscopic and barium enema X rays in Nottingham. Colonoscopy is the first choice of investigation in Nottingham although a small number of patients are unsuitable and hence are investigated by the radiological technique. Including staff, equipment, drugs, disposables overheads and admissions colonoscopy costs £106 compared to a barium enema at £50 per investigation. These are expected costs since they are based on average excision and admission rates.

Drawing all this data together in the model determines the total cost and yield for the F.P.C. area. In the initial screening round , the total N.H.S. cost of the programme is just over £23,0000; with 50% of the costs attributable to the screening process, 30% to diagnostic investigation and 20% to administration. The yield is 100 cancers and 324 adenomas, of which 115 are larger than 2 cms and hence at greatest risk of becoming malignant. In subsequent screening rounds the total cost declines to £211,500 in the second round and and £136,000 in the third round. This is due to the fall in the number of people to be screened only - acceptors at the previous screen are reinvited and the decline in the positive rate. In addition the administrative workload declines slightly as an accurate population register is built up. The corresponding yields are 68 and 55 cancers respectively.

The performance of the Haemoccult test while comparing favourably with alternative techniques is known to misclassify not only people who have cancer(sensitivity) but also people who have no bowel disease (specificity). Various options for improving performance have been investigated all of which have economic implications.

Sensitivity can in theory be increased by extending the test period or by altering the chemical properties of the test.

The Nottingham trial has investigated the effects of testing over six days instead of three. In such a comparison the additional costs must be compared with the additional yield. Applying the relevant parameters to the F.P.C. population model suggests total costs of £370,000 (61% higher than three day testing) with 11 more cancers detected. It should be stressed that the difference in the yield in the Nottingham study is not yet statistically significant on statistical tests.

Another way of increasing Haemoccult sensitivity is to rehydrate the completed tests prior to development , although this gives more positive results. While the technique has not been used in Nottingham data is available from a smaller randomised study in Sweden. Applying these figures to the Family Practitioner Committee model suggests total costs are almost doubled in comparison with unhydrated tests while 31 more cancers would be detected. The same criteria of comparing additional costs and yield must be used in a comparison of the techniques.

The Haemoccult test can also misclassify healthy people due to dietary factors. In Nottingham the effect of inviting those with a positive test to perform another test with a restricted diet prior to investigation has been studied. By only investigating those remaining positive after retesting the number of people undergoing unnecessary investigations can be substantially reduced. The model described above includes retesting of initial positives with dietary restrictions. Without retesting , investigation costs would be tripled. The costs of retesting positives is £2,250 while 940 colonscopies are avoided at a saving of approximately £100,000 however between one and two true positives ie cancers in the population retest negative and hence are missed by the programme. This `cost' must be weighed against the avoidance of unnecessary testing.

In summary Haemoccult performance can be improved but only at the cost of more unnecessary investigations in the case of improving sensitivity or of missing more cancers in the case of improving specificity.

3. Treatment consequences

The monthly work load for the hospital serving a F.P.C. population in the model described above would be 24 positive tests to investigate and 4 cancers to treat. Based on a comparison with the unscreened group in Nottingham this represents an increase in the the number of operations of about 50% in the first two years which may be offset by a reduction in future operations. There is evidence in Nottingham that the number of operations in each group is roughly equal in the fifth and sixth year after screening commences.

If screening detects earlier stage cancers, some treatment cost savings may be expected. More screen detected cases can be treated at the colonoscopy stage thus avoiding the need for more expensive surgery. In the Nottingham trial 24% of screen detected cancers have been treated endoscopically compared with 2% of those presenting symptomatically. Initial work on trial data indicates that Stage A cancers are on average cheaper to treat than Stage B and C due largely to the possibility of endoscopic removal.

It is important to stress the large variations in hospital costs within a particular cancer stage as well as between stages. Accordingly costing is of a large sample of the cases arising from the Nottingham trial to overcome the problem of variation. Early estimates of the hospital costs where polypectomy is not possible range from £2030 to £3430 for stage A and C respectively . These figures are based on 220 cases and include follow up to the end of 1989. Some stage D cancers also have very low treatment costs because they die shortly after admission indeed some die with no hospital treatment at all . Where no operation is performed median costs for this group are £770 while for those undergoing an operation the median cost is £3080. While these estimates are extremely crude they give some indication of the orders of magnitude involved.

DISCUSSION AND CONCLUSION.

So far costs per cancer detected have not been quoted since these invite comparisons with other cancer screening programmes in an inappropriate manner . Their only use is in comparing alternative ways of screening for cancer of one particular site. The principle objective of cancer screening is health improvement hence ideally the cost per unit of health gained is the appropriate final outcome measure eg. cost per life year saved. Unfortunately life year data is not available at this stage of the research.

Patient costs have not been included . Data collected so far suggests time and travel costs are incurred by the screening programme in the region of £5 per person per clinic and £20 per investigation although these would have to be offset against shorter expected length of hospital stay. Owing to the age of the population covered the value of time off work has not yet been found to be significant.

In conclusion the figures presented above are estimates of the cost and the workload consequences of implementing the Nottingham protocol in a F.P.C. area. Until data on benefits are available this will remain a partial evaluation , indicating the relative efficiency of Haemoccult screening protocols without commenting on overall cost effectiveness. A comparison with alternative uses of the same resources in terms of costs and benefits must be made prior to any such judgement.

THE PATIENT'S VIEW

Mr W C Reynolds, Member, British Colostomy Association

I underwent an operation for the removal of a cancer of the rectum in June 1984 at the age of 64. The operation was entirely successful and I have had no problems with my stoma, in fact, I feel better now than for many year. There is little I cannot do, although I take no chances and will undertake nothing that means straining. I have a parastomal hernia which tends to get in the way when bending but wearing a wide ostomy belt helps this.

At the time of my operation there was no stoma care nurse attached to the hospital but I received valuable assistance from the representative of an ostomy equipment manufacturer. When after 6 months I finally decided on the make of bag or pouch to suit me, I received a great deal of support from the representative who was infact my only source of practical information.

More than a year from the date of my operation I was accepted as a Visitor for the British Colostomy Association. This association provides free guidance, assistance, counselling and information to all people with colostomies.

This paper recounts my own experiences as well as some of those people with colostomies.

Most of the people I have visited in my capacity as a British Colostomy Association visitor have made a very good recovery with few problems. Many of them have been fortunate in having good support at home, and in particular to have the services of a skilled stoma care nurse. They have learnt to accept their stoma and come to terms with all that it means.

However, the time of diagnosis is often the most difficult period. Most people usually go to their general practitioner with their first symptoms. These may include stomach pains, diarrhorea, difficulty in passing motions, explosive passing of faeces, wind, blood in faeces, generally unwell feeling, headaches, loss of weight, lack of energy and great desire to sleep. Often the initial visit to the general practitioner results in reassurance that the symptoms are probably due to a bowel virus, colitis or haemorroids. For many, it seems, referral to hospital was delayed. Sadly, some people report they had no physical examination of abdomen or rectum before referral to hospital for expert examination. Increasing pain and discomfort often resulted in low morale and this was compounded by the shock and despair of finally being informed that the problem was bowel cancer.

When people were told their diagnosis some thought they would certainly die, others that they would be invalids for the rests of their lives and a few thought simply of giving up. In all cases it is my impression that lack of information in the early stages did not help these feelings. It would seem desirable that any patients presenting with bowel symptoms should, if there is no improvement, be referred to the local hospital for expert examination, without delay. This may help the deteriorating morale and consequent despair of the diagnosis for the person.

Cancer sufferers to whom I have spoken have often said that an explanation of what is involved in the surgical removal of a cancerous bowel or rectum, and why it is necessary, would be useful in helping the patient to accept what has to be done. I myself was told what was involved, where I would be cut etc and I found it helpful. I knew then that the bad part would be removed and that, apart from wearing a bag on my abdomen, life would continue more or less as usual.

However, I was 64 years of age.

If a younger man wished to have a family then there may be additional problems. Many people who have undergone abdominal surgery, can experience sexual difficulties after their operation. In the male patient, nerve damage may inhibit an erection and the ability to ejaculate, thus precluding the possibility of future fatherhood. Surely, the patient should, before the operation is carried out, be informed of these possible problems. Indeed his wife or partner should also be informed and if children are desired in the future, use could be made of a sperm bank. Such action could avoid disappointment and in extreme cases prevent the breakdown of the relationship. In women, excision of the rectum results in a change in pelvic anatomy. Intercourse can be both unsatisfactory and painful. Again this should be made known to the female patient before operation, in order to help prevent troubles at a later date. There is an excellent organisation which can provide counselling for sexual problems and whose services are offered free of charge. This fact should be made known to all those undergoing bowel surgery.

It is vitally important that the person who is to undergo surgery for a colostomy, is assured that he or she will remain the same person. They are the same person and always will be to their friends and to those who love them. They must be encouraged to know that they are not alone and that there is support in plenty if needed. For colostomy patients, from the time of the operation a bag or pouch will always have to be worn on the abdomen. This must be thought of as a part of them, and they have to be persuaded to come to terms with it and with the fact that what used to be evacuated discreetly and under control from the rear, will now move uncontrolled into the bag on the abdomen. The patient must be assured that it will not be easily visible beneath clothing and that with modern bags the risk of odour is absolutely minimal. It is important for the well being of the patient and the patient's family that this is well known. It can prevent a lot of worry and unhappiness.

Diet also is scarcely affected and again there is information available at no cost to the patient.

There is also the homo-sexual to consider. At the moment there is little literature to be found concerning the effect of a colostomy or surgically made stoma on these individuals. The same treatment and advice regarding the actual operation is unchanged but the condition of such a patient after the operation is one which can cause considerable anxiety. This may be of particular significance if the patient has indulged in penetrative sex with his partner. Following operation this may well be impossible and of course penetration into the stoma must be forbidden. The patient and his partner must be given a thorough explanation of what has happened and how this could

affect their future sexual relationships. In addition there may well be psychological problems ensuing that cannot be overlooked.

A further very important matter is siting of the stoma. Good practical placement of the stoma can minimise future problems. As much information as is possible must be obtained from the patient regarding sporting activities, hobbies, occupation, position of body whilst working, type or style of clothing. All these matters should be discussed with the patient.

Again the patient's culture must be considered as the site of the stoma can be of considerable importance in some religions. It may be more acceptable for the stoma to be sited above the waist for some people, as siting below the waist can be considered 'dirty'.

In the first few weeks after leaving hospital, a visit by the stoma care nurse or a community nurse experienced in stoma care is almost certainly to be welcomed. The knowledge that there is care and support is of considerable benefit to the patient and to his or her family. The services of the self help groups ought not to be ignored as, good practical help can be given by people who themselves have had similar operations and are experienced in the management of stoma care. Self help groups like the British Colostomy Association may be of service to the patient if required but of course a Visitor from the Association should always keep in touch with the stoma care nurse on the case - if there is one. It is important that, until the patient feels that he or she can manage adequately and has no fear or reservation concerning the management of the stoma, there is full assurance of complete support.

For some people there is an excellent system of support available from the start, but others may live in isolated areas where there may not be such good support. A code of practice could be developed to ensure that back up would be available automatically to all patients. This would mean linking family doctors, stoma care and community nurses and self help groups.

The most important item of management cannot be overstressed. It is communication. Patient, doctor, hospital, stoma care/community nurse, self help groups are all involved. When a person is found to have cancer of the colon or rectum everyone must work together to the benefit the patient who is after all the person who matters.

Although this kind of communication may take time to reach fruition, in the end it could prove a useful weapon in the fight against this form of cancer and thus be both clinically and economically viable.

TREATMENT OF ADVANCED DISEASE

Richard Begent, Charing Cross and Westminster Medical School, London

About half of patients with colonic or rectal carcinoma have an unresectable primary tumour or develop metastases or local recurrence. Management may include resection of localised disease, chemotherapy, radiotherapy and no antitumour treatment.

There is much evidence that resection of localised tumour can be curative. August et al (1984) estimated that of patients with recurrent or metastatic tumour, 4% can be cured by resection of local recurrence, 2% by resection of liver metastases and 1% by resection of a lung deposit. There is evidence that recurrence is more likely to be resectable if it is detected at an early stage. Early detection of recurrence is assisted by frequent measurements of serum carcinoembryonic antigen (CEA) levels. 12-40% of tumours detected in this way are resectable. 5 year survival after such resection is up to 30% (Martin et al 1985). It has not, however, been shown that CEA-promoted second look surgery improves survival compared with conventional follow-up in which the surgeon is free to resect a recurrence if he locates it by other means. A randomised trial is in progress to investigate this question supported by the Cancer Research Campaign. 1100 patients have been entered and it is likely that an answer will be obtained. Pending such results it is proposed that the chance of long term survival after resection of recurrence justifies the follow-up and risk of an operation for unresectable disease.

Localised but unresectable deposits of colorectal carcinoma respond to radiotherapy with pain relief in at least 80%. Medium term disease control is often possible locally.

Cytotoxic chemotherapy is the only practical form of treatment for the majority of patients with advanced colorectal cancer. However, generalised application has not been accepted because an overall survival benefit has not been shown compared with no treatment. The very large randomised trials needed to tell whether there is survival benefit have not been done with the most effective modern treatments. Some metastatic carcinomas of the colon and rectum progress very slowly without treatment whilst others are lethal in a few months. Objective tumour responses to chemotherapy do occur and are commonly sustained for 6-12 months. 5-fluorouracil (5FU) is the most effective single drug with response rates commonly reported in the range of 5-30%; the effects appear to be does related. The drug is better tolerated when given by long term intravenous infusion than by bolus injection and may be more effective (Fiscus 1987, Lokich et al 1989). When metastases are confined to the liver, 5-fluorodeoxyuridine, a drug closely related to 5-FU, infused into the hepatic artery gives higher response rates than intravenous administration but produces liver toxicity (Chang et al 1987). The UK hepatic artery pump trial is investigating whether there is survival benefit and alteration in quality of life by comparison with a palliatively treated control group (Allen Mersch 1989).

Intravenous folinic acid combined with 5-FU gives higher response rates than 5-FU alone (Petrelli et al 1987, Erlichman et al 1988). It commonly causes dose-related diarrhoea. However, this is the most effective regimen in general use giving objective responses in 30-49%

of patients and symptomatic relief in up to 75%. Randomised trials are needed to investigate whether there is survival benefit in asymptomatic patients. Many series show longer survival for patients having an objective response to chemotherapy by radiological or tumour marker criteria (Laufman et al 1987, Hine et al 1984, Al Sarraf et al 1979). it may be argued that the responding patients were a group destined to have longer survival regardless of therapy. This view is not convincing for patients whose symptoms are relieved by chemotherapy and who returned to a normal life. It is appropriate to offer chemotherapy to patients with symptoms or with evidence of progressing disease likely to produce them within a few months. Chemotherapy should be stopped if it is not producing evidence of response after 8 weeks or if quality of life deteriorates and cannot be restored by changes in the regimen. Treatment is best monitored by clinical parameters, appropriate radiology and serum tumour marker levels. Serum CEA measurements are the most useful but CA19/9 and others may also be of value (Begent and Rustin 1989).

The high level of resistance to cytoxic drugs makes investigation of other forms of treatment for colorectal carcinoma a matter of urgency. Antibody targeted therapy in which a radionuclide, toxin or cytoxic drug is delivered selectively to the tumour or in which natural effector mechanisms are activated at the tumour site have eradicated human colon carcinomas grown in mice and produced responses in patients (for review see Begent 1990). Cytokines, a heterogeneous group of proteins with a wide variety of cell regulatory, immune and inflammatory properties are being investigated for therapy of cancer. Responses in colonic and rectal carcinoma have been reported with variety of different approaches (for review see Kelly et al 1990). These technologies are at an early stage of

development and it is likely that the systems can be improved with benefit to patients with cancer of the colon and rectum.

There is much that can be done for patients with advanced colorectal carcinoma. this is best achieved if the patients are followed up after their initial operation by a team skilled in this area. Reassurance will be gained by patients who are well informed and know that whether they relapse or not they are in the hands of a knowledgeable team.

LIVER RESECTION IN ADVANCED DISEASE

Myrddin Rees, Basingstoke District Hospital

Within five years of presentation up to 50% of patients with colorectal cancer will have recurrent disease with the liver as the most common site of secondary spread. Of this group with tumour recurrence about 20% will have deposits apparently confined to the liver. These patients are amenable to regional therapy such as intra-arterial therapy, cryotherapy, laser therapy, or surgical excision. When surgery is feasible, it offers the only chance of cure, albeit in a small number of cases. A number of centres have now reported large series with between 25-40% survival five years after liver resection for secondary disease.

Before advising surgery, a number of criteria need to be considered. First, is the disease confined to the liver? Though this would seem to be straightforward, unfortunately, current imaging techniques often under-estimate the true extent of disease. However, by employing a combination of contrast enhanced CT scanning of the abdomen and chest, pre-operative ultrasound, isotape bone scans (if the patient has bone pain) and routine use of computed arterial portography, we have reduced our non-respectable rate from 25% to less than 5%. In other words, by our more aggressive pre-operative investigations we have avoided the disappointment of an unnecessary laparotomy.

If the disease is confined to the liver, can it be removed? Although the best results are obtained with truly solitary metastases, there are a number of encouraging reports demonstrating 25% survival at five years after excision of multiple, unilateral or bilateral metastases.

In the absence of any other effective modality we currently respect hapatic deposits as long as this can be achieved with a curative margin and also leave enough functioning liver tissue - usually equivalent to a minimum of 30% of a healthy liver. Other factors that may influence this decision are that Duke's B patients will do better than those with Duke's C disease and patients with a long disease free interval have a better outlook.

Having decided that an operation is feasible, the patient is assessed and counselled regarding the risk of the operation. In a healthy individual the risk of standard hepatectomy should be minimal and equal to or less than the risk of operating on the colon or rectum. Occasionally, patients present with massive deposits or caudate lobe tumours that may require grafting of the inferior vena cava and complex bile duct reconstruction. The risk in these cases is much higher but often acceptable to the patient facing an imminent painful death. Our only two operative deaths out of 44 hepatectomies occurred in this category. The motivation for such relatively high risk procedures usually comes from a fully informed patient. If patients have less advanced disease the natural history may remain favourable for some years and we counsel a more conservative approach initially. However, most patients prefer and encourage active intervention and thereby remove uncertainty and doubt. If surgery is feasible and accepted, our first task after laparotomy, prior to resection, is to document the true extent of disease using careful palpation and intra-operative ultrasound. If there is peritoneal disease or large,

malignant hepatic nodes confirmed by frozen section, the planned resection is abandoned. If our initial inspection shows that all the detected disease can be excised, the resection is carried out. Using the ultrasonic suction device (CUSA) and argon beam cautery (Beamer 1) the resection can proceed in a safe, controlled manner with minimal blood loss. The patients usually spend one night in intensive care and are discharged between 7-10 days, depending on the length of their homeward journey. The subcostal wound is well tolerated and their recovery compares favourably with that following any bowel procedure.

The advantage of surgical excision in the small percentage who are suitable is that it removes all detectable secondaries without the need for further interference. The patients who are not amenable to excision are invariably grateful that someone made sure their disease could not be removed. The patients who have had resection leave hospital free of disease with the hope that they may be one of the fortunate 25% who survive five years and beyond. The majority of the others will survive for more than two years in good health.

We believe that this approach offers a cure to some patients, prolonged hope and improved quality of life to others and to an unfortunate few, at least the reassurance that all possible care has been taken.

ADJUVANT RADIOTHERAPY IN RECTAL CANCER

By Dr S J Arnott, Consultant Radiotherapist

The use of adjuvant radiotherapy in rectal cancer remains controversial in spite of the fact that there is growing evidence to suggest that it may reduce local recurrence rates in certain patients. There is as yet no clear evidence that it improves survival rates.

The first reports of the use of adjuvant radiotherapy in patients with rectal cancer came from the Memorial Hospital in New York following a retrospective review which had been carried out on patients who had received short courses of low dose pre-operative radiotherapy. This review suggested that patients with Duke's C disease had a significantly lower incidence of local recurrence if they were given pre-operative radiotherapy. A subsequent randomized controlled trial did not confirm this benefit. Nevertheless, this trial stimulated a great deal of interest in the USA and the Veteran's Administration Surgical Adjuvant Group subsequently embarked on a further randomized trial, once more investigating the use of low dose pre-operative radiotherapy in patients with rectal cancer. The doses used were 2,000 - 2,500 cGy delivered in 10 treatments, with surgery to follow as soon as possible after the 10th fraction of radiotherapy. Overall, there was no significant improvement in survival in this study but sub-group analysis showed that patients who were treated by abdominoperineal excision had a better survival if they had received pre-operative radiotherapy. Statistically, such an analysis is invalid and this trial therefore

remains inconclusive. However a number of biological effects of radiotherapy were noted in this study. In particular, it was found that in patients who had received pre-operative radiotherapy, there was a statistically significant reduction in the incidence of lymph nodes involved by tumour found in resected specimen.

At about the same time as this trial was being conducted, a further trial of pre-operative radiotherapy was being investigated in Toronto where a slightly different treatment was being used. At this centre, a single dose of 500 cGy was given immediately prior to planned surgery. In this trial too, it was only when sub-group analysis was carried out that an advantage of pre-operative radiotherapy was found. In patients with Duke's C disease, it was claimed that the single pre-operative treatment led to improved survival. Once more, such an analysis is open to question from a statistical point of view.

In an attempt to try to provide a definitive answer regarding the question of low dose pre-operative radiotherapy, the Medical Research Council embarked on a multicentre study in which patients managed by surgery alone were compared with those who had received either a single dose of 500 cGy immediately prior to operation or a dose of 2000 cGy in 10 treatments. When this trial closed in 1978, 824 patients were available for analysis. Once more a number of definite biological effects of pre-operative radiotherapy were discovered but when the overall survival rates were compared, there was no significant survival advantage in either of the groups which had received pre-operative radiotherapy.

Analysis of the results did show however that there was a very strong relationship between tumour mobility and prognosis and those patients who were found to have tethered tumours fared significantly worse than those with mobile lesions. This is a feature which may be determined clincally pre-operatively and it was felt therefore that this group of patients who have a poorer outlook following surgery should form the basis of a second trial in which a higher dose of pre-operative radiotherapy would be given. This became the second MRC Rectal Cancer Trial.

Recruitment to this study has been poor, largely on account of surgical difficulty in defining patients eligible for inclusion. As a result, this trial has now closed having failed to accrue the necessary numbers of patients to achieve statistically meaningful results. However, it has shown a trend towards a reduction in local recurrence and improved survival, although the differences were not statistically significant. There was however a significant reduction in the incidence of metastases in patients receiving pre-operative radiotherapy. Many other centres throughout the world have looked into the use of pre-operative radiotherapy but given in slightly different ways. They have investigated giving short courses of treatment using daily doses of 500 cGy to a total of between 1,500 cGy - 2,500 cGy. Many of these studies have reported reduced local recurrence rates and in two, there is a suggestion of improvement in survival. At the present time, it is not possible to be clear about the benefit of pre-operative radiotherapy nor is it possible to define an optimal way in which pre-operative radiotherapy should be given. This is however an important question and one which needs to be answered. The new Axis Trial which has recently been launched should hopefully provide a definitive answer.

In recent years, post-operative radiotherapy rather than pre-operative treatment has been investigated in certain patients who are known to be at greater risk of developing local recurrence. This can often only be determined following examination of the resected specimen. Hence it has been felt more logical to give post-operative radiotherapy to such patients. These patients are those with Duke's B & C disease. In addition they also have a worse survival than patients with Duke's A tumours. Such patients have been investigated nationally in the United Kingdom and Ireland in a Third Medical Research Council trial. Patients receiving post-operative radiotherapy were compared with those managed by surgical excision alone. Recruitment to this trial has been much better than the second study and it has now closed. Already analysis of the results shows a significant reductions in local recurrence rates but as yet no clear survival advantage in patients given post-operative radiotherapy.

Other studies of post-operative radiotherapy have ben carried out in the USA and other parts of Europe. These all show a trend towards a reduction in local recurrence rates although no clear cut survival advantages. However, a reduction in local recurrence is important to patients. It is the cause of a great deal of distress, in particular pain which may be difficult to control. Frequently, local recurrence is simply part of a more generalised recurrence of the disease. This implies that reducing local recurrence is only likely to make a small impact on overall survival in patients with rectal cancer. However, the very difficulty of dealing with local recurrence, either surgically or by means of radiotherapy justifies attempts to reduce its incidence as this will contribute greatly to the quality of life of many patients.

approach has been suggested. This would involve, for example, adjuvant portal vein infusion to try and reduce the incidence of liver metastases combined with either pre- or post-operative radiotherapy to reduce the likelihood of local recurrence of rectal cancer. This approach is currently being addressed in a large multicentre trial (the AXIS trial).

Although the rationale for adjuvant cytotoxic chemotherapy is sound the timing and method of delivery are still controversial. Patients are in a most vulnerable state during the early postoperative period. Circulating malignant cells are likely to be present, the patient is immunosuppressed as a result of anaesthesia and the well known hypercoagulable state may contribute to the development and growth of micrometastases particularly in the liver. Accordingly if adjuvant cytotoxic therapy is to be used in the most effective manner possible it should be given peri-operatively in as high a concentration as can be tolerated by the patient.

Careful selection of patients is also most important. In general patients with Dukes A and D disease are unsuitable for adjuvant treatment whereas patients with Dukes B and early Dukes C are at high risk of recurrence and might benefit from an effective adjuvant approach.

In conclusion there is still little indication for recommending routine adjuvant systemic chemotherapy outside the confines of clinical trials. Whether adjuvant cytotoxic portal vein infusion will be of value depends on the results of on-going randomised trials.

INTERNATIONAL VARIATIONS IN CANCER SURVIVAL RATES

Dr Tom Davies, Addenbrookes Hospital

There are quite marked differences both between and within countries in the survival rates for most cancers, in particular those cancers with survival rates around 30%-60%.

International differences

Hanai illustrated the differences between Japan, the USA, England and Wales, Norway, Finland and Iceland. The figures used are relative survival rates. The relative survival rate is the survival rate of a group of cancer patients, usually defined by age group and sex, adjusted for their probability of dying from causes other than cancer. The older the group of patients, the greater the chances of dying from other causes and therefore the greater is the effect of adjustment to their crude survival rate.

Comparable figures on natural survival rates are not published as often as one might expect and of course cannot be published for at least five years after registration. Therefore some of the data used here are quite old, but for cases registered as late as 1973 and followed up until 1978, survival was about 50% better for cancer of the colon and rectum in the USA white population than in England and Wales. Other countries were in intermediate positions (Fig. 1).

At a later period cases registered in the USA between 1977 and 1980 had survival rates of 52% and 50% for cancers of the colon and rectum, but by 1979 in England and Wales these figures had only risen to about 35% (Fig. 2).

On the whole, sex differences are small and not very consistent. In earlier data women seemed to do slightly better than men, but this position is reversed in more recent figures.

As one would expect for most cancers older people have poorer survival rates, but this is not true for the US white population, at least up to the age of 75 (Fig. 3).

Regional variations

Just as there are international variations there are some differences between the regions and countries within the United Kingdom. For cases registered in 1970-73 Scotland always has better figures than England and Wales, but the interregional differences are much smaller (Fig. 4).

In the 5 years following diagnosis the probability of dying is not the same in each year : most deaths occur in the first year (Fig. 5).

Possible explanations

Such apparently large differences, particularly between international figures, demand some explanation. These fall into three main categories.

artefacts

factors not related to treatment

treatment

Artefacts

Apparent differences can be created by

a) not measuring survival from the same point (Fig. 6)

b) lead time bias (Fig. 7)

c) incomplete reporting, with differing proportions of cases being registered from death certificates (Fig. 1)

d) validity of diagnosis

Non-treatment factors

If the differences are real they may be due to a number of factors which may influence the natural history of the disease and the type of treatment given but are not under the control of clinicians.

e.g. age
sex
stage at diagnosis
histological type
social class
marital state
concurrent disease

Data on age and sex are about the only data that are easily available. Stage at diagnosis may differ between groups but in general, information about this is sparse. An additional problem is that different staging methods may be used for different cancers, and also for the same cancer in different registries. In addition retrospective coding is a skilled technique and performance may vary.

The proportion of "localised" tumours has been used in an analysis of data from four countries (Fig. 8). For the USA, Norway and Finland this is about 35% but in Japan the proportion is smaller, but this does not appear to make a dramatic difference to survival in Japan.

Treatment factors

Although it is apparent that the access to medical care and its effectiveness when applied may vary, there is little evidence that differences in modes of treatment are responsible for regional or international differences in survival. It is a solution that is inferred if they cannot be explained by anything else.

The East-Anglo Danish study

These differences clearly merit closer investigation not only to see if they are real, but if they area, to produce some kind of explanation.

East Anglia has a population of just over two million and in the past there have been a number of cancers in which survival has been poor when compared to other countries. Cancer registration in Denmark covers all of their 5 million population and the data they collect are similar enough to those collected in East Anglia to make a proper study feasible (Fig. 9).

The study is divided into two phases.

The first phase which has already started, is intended to see if the differences still exist. Data will be limited to those available in the cancer registries namely:

Identity

Starting points for survival

Date of onset on symptoms

Date of first consultation (second choice for survival time)

Date of first hospital attendance (first choice for survival time)

Date of diagnosis

Cancer classification

Staging - local, regional nodes, distant mestateses

Death - date and cause if known

Referral pattern - by whom seen

(Fig. 10)

The central year of registration for 5-year survival will be 1984, but with "spread" each side to get the necessary 500 cases (Fig. 11).

However a separate population of cases registered in 1989 will also be studied to see if the variables recorded in the 1984 population were approximately the same five years later.

If the differences still exist Phase II will be entered. This will be done on the same patients, but more data will be collected on:

concurrent disease

treatment

modes and place of care

Fig 1 .

HANAI & FUJIMOTO

Comparison of five-year survival rates for cancer patients by sex and site in seven populations in six countries

Site	Sex	Five-year relative survival rate (%)							
		Japan Osaka*		USA SEER*		England & Wales*	Norway*	Finland*	Iceland*
		DCO cases* Incl. (1975-1977)	excl.	White (1973-1979)	Black	(1971-1973)	(1971-1973)	(1972-1975)	(1970-1974)
Colon	M	27.3	34.7	47	41	29.6	40	32.3	32
	F	25.6	34.6	49	46	29.4	41	31.2	29
Rectum	M	24.6	31.7	44	28	30.8	36	28.3	25
	F	22.8	29.7	47	41	32.9	40	32.1	38

Fig 2.

COMPARISON OF FIVE YEAR SURVIVAL RATES FOR CANCER PATIENTS DIAGNOSED BETWEEN 1979 AND 1981 (percentage)

Site	Canada	USA	S. Australia	England and Wales
	(crude)* 79-81	77-80	77-85	79
Colon	M 38 F 42 (colorectal)	52	48	36 34
Rectum	M F	50	50	37 35

* relative survival could be expected to be about 5% higher

Fig 3.

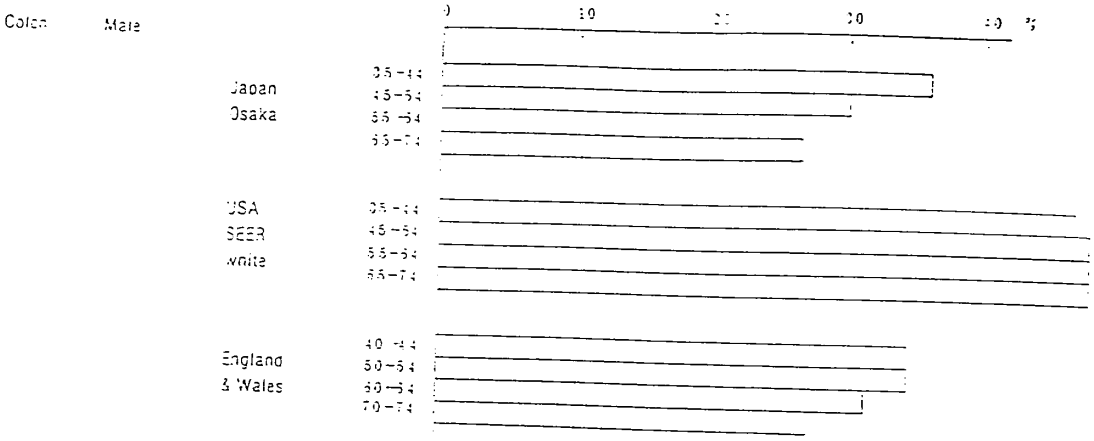


Fig 4.

FIVE YEAR RELATIVE SURVIVAL UNITED KINGDOM 1970-73

COLON

	M.	F.
England and Wales	30	29
Scotland	33	36
Cambridge	22	25
Mersey	22	25
South Thames	25	28
West Midlands	27	29

RECTUM

England and Wales	31	33
Scotland	35	35
Cambridge	27	33
South Thames	27	29
West Midlands	27	30

Fig 5.

GRAPH A Relative survival rates, all cases

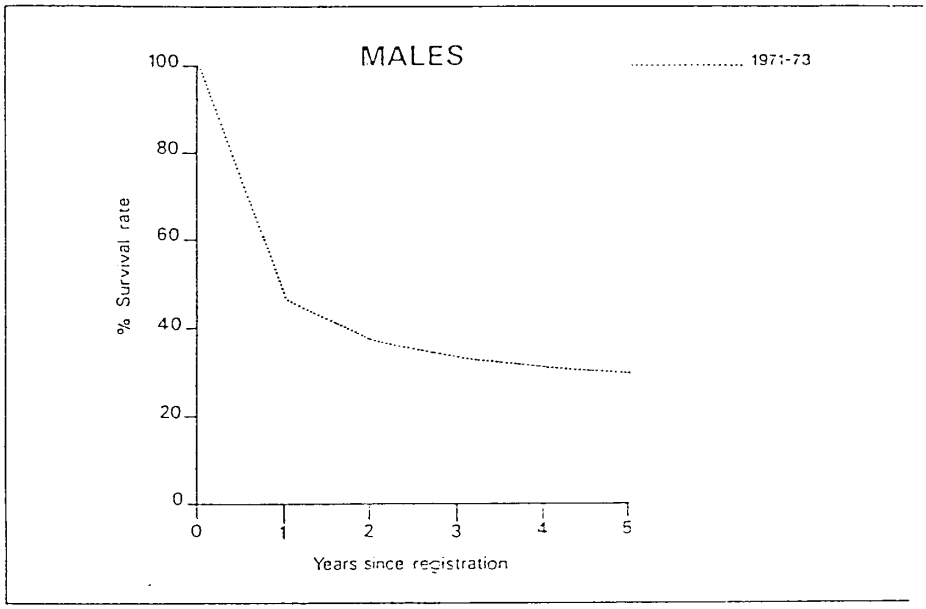


Fig 6.

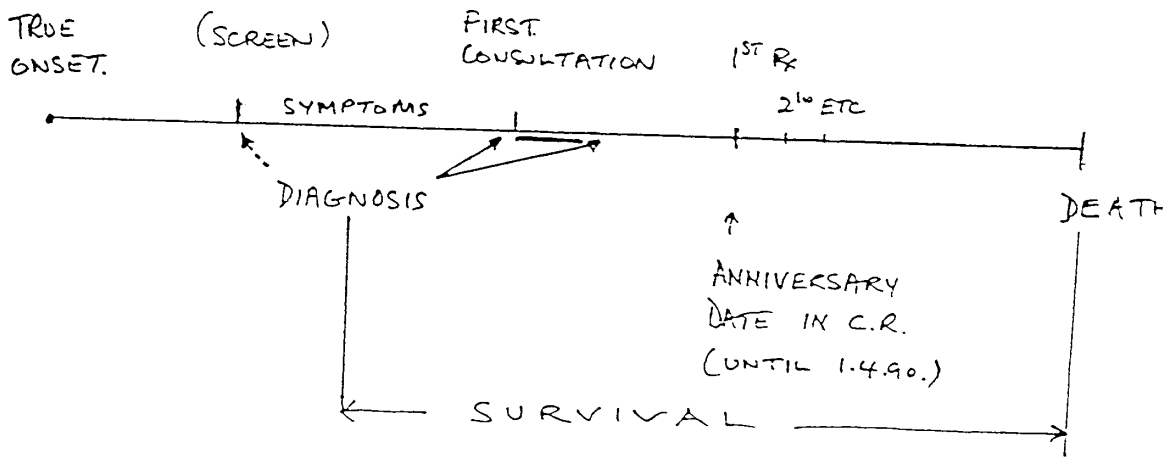
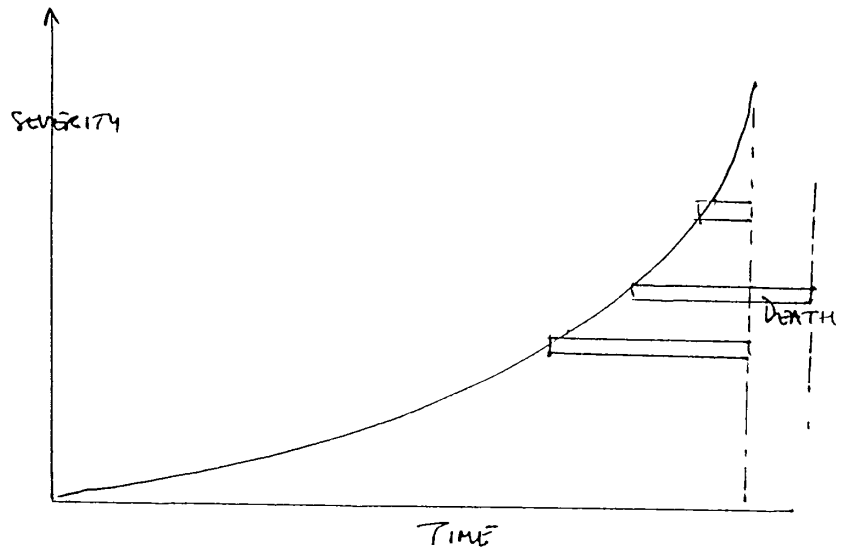


Fig 7.



LEAD TIME BIAS

Fig^8.

Proportion of localized cases and their five-year relative survival rates*

Site	Sex	Japan Osaka (1975–1977)			USA SEER (1964–1973)				Norway (1968–1975)		Finland (1953–1974)	
		A		B	White		Black		A	B	A	B
		DCO cases			A	B	A	B				
		incl.	excl.									
Colon	M	13.0	18.7	76.0	35	77	30	66	37	68	34.1	59.3
	F	11.6	19.8	65.4	33	80	29	61	35	69	35.3	59.5

A: % of cases localized; B: five-year relative survival rate (%)

Fig 9.

5 year relative survival	colon m	colon f	prostate	cervix	ovary
England & Wales (reg 70-73)	30	29	36	54	25
(reg 78)	32	30	38	52	25
(reg 79)	36	34	45	53	26
Cambridge (reg 70-73)	22	25	37	55	29
Denmark reg 78-82	38	40	51	71	37

Fig 10.

The East-Anglo Danish Study

Identity

Starting points for survival
- Date of onset of symptoms
- Date of first consultation (second choice for survival time)
- Date of first hospital attendance (first choice for survival time)
- Date of diagnosis

.../

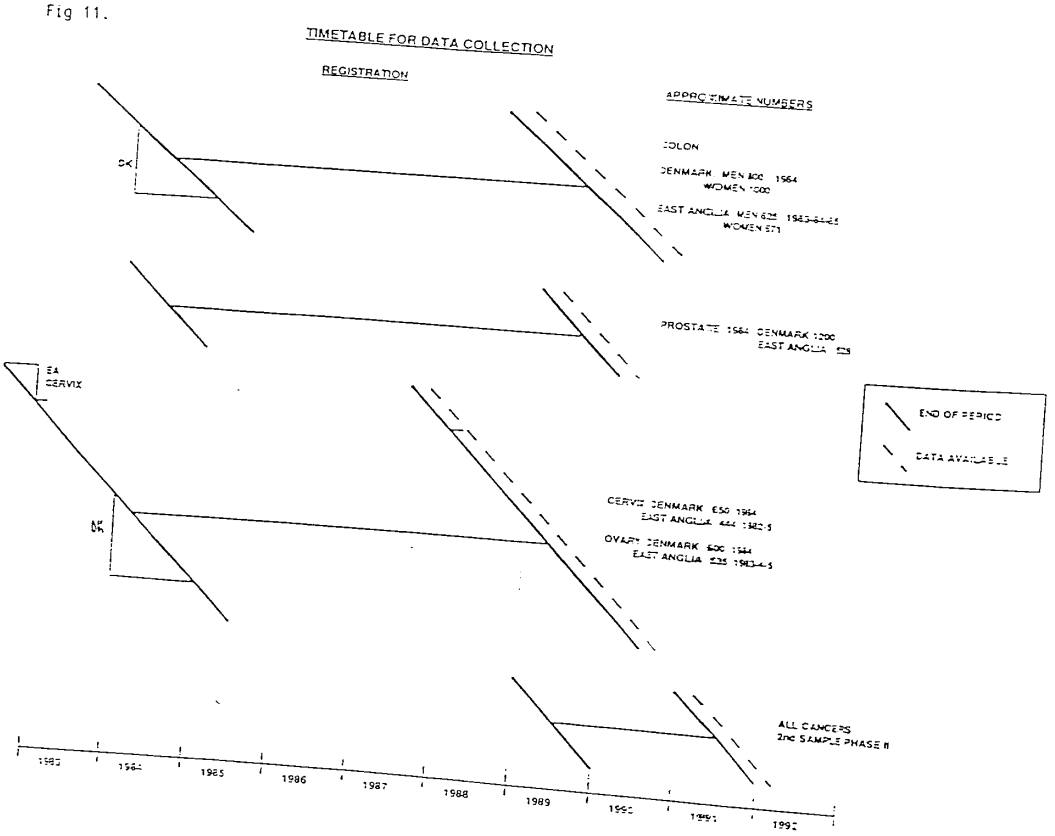
Cancer classification

Staging - local, regional nodes, distant metastases

Death - date and cause if known

Referral pattern - by whom seen

Fig 11.



CLINICAL FACTORS THAT INFLUENCE OUTCOME

AFTER COLORECTAL CANCER SURGERY

Mr Robin Phillips, Consultant Surgeon,

St Mark's and St Bartholomew's Hospitals

Patients who came to surgery with colorectal cancer either have obvious distant spread of their disease at the time of presentation or they have apparently localised disease. The latter group are then said to have undergone a "curative" resection, but experience has shown that quite a number of these so-called "curative" cases actually already have subclinical occult hepatic metastases and are therefore incurable by therapy means that when comparing the results of one surgeon with another, or the results of one operation with another (for example, in rectal cancer surgery, comparing restorative operations without a permanent colostomy with excisional operations that result in a permanent colostomy), or even comparing the results of surgery with and without a local adjuvant treatment such as radiotherapy, one cannot expect that factors such as occult hepatic metastases at presentation (which lie outside the treatment field) will be influenced by the choice of surgeon or treatment. This means that for local treatment strategies longer term survival is largely irrevelant. Indeed, if large differences in survival are claimed for local treatment modalities, this should stimulate a healthy scepticism as to whether the different treatments were ever inherently comparable.

From the above discussion, it can be readily appreciated that the main aims of clinical activity must be to achieve as low an in-hospital mortality as is possible, to avoid local treatment failure, and to give the best possible functional result/quality of life. It might of course be argued that to prevent local recurrence (by better surgery or by adjuvant radiotherapy, for example) might in the longer term be translated into a survival benefit because metastases could arise from an unnecessary local recurrence and cause death.

This is true only up to a point. In most cases where there is local recurrence (and especially when the surgery has been conducted to a very high standard) there is simultaneous distant recurrence which means that the prevention of the former would not have influenced subsequent longer term survival. Furthermore, in the case of radiotherapy an analysis of trial results done at around 5 years (as virtually all of them have been done) will have a systematic bias in favour of active treatment because the serious disadvantages of radiotherapy take rather longer to appear. This means that any marginal effect in the reported literature in favour of radiotherapy must inevitably become less as analyses with longer follow-up are reported.

Returning then to the factors which can be influenced by routine clinical activity, the Confidential Enquiry Into Perioperative Death (CEPOD) pointed out the advantages of: specialisation; the input of senior clinicians into patient management, particularly in emergencies; and the importance of lack of haste and adequate resuscitation before taking the patient to theatre These are largely organisational and management

recommendations, although there are clear revenue consquencies to expanding the numbers of specialists; allowing sufficient numbers of consultants that they might participate in emergency activity at night and yet still have time off the next day to recover; and supplying dedicated daytime emergency operating theatres so that semi-urgent cases can be done by a team who have had some sleep and who have the back up of a fully functioning hospital and all its services.

In large bowel cancer, elderly patients, particularly when they present with large bowel obstruction, seem to do very badly. Not a lot can be done about their age, but the management of their obstruction could be improved upon. In one study, one-stage emergency resection done by a senior team had half the mortality rate of more junior doctors (13% versus 24%). From the same study, the overall mortality for patients with obstruction was about 1 in 5 rising to 1 in 3 in the elderly.

Similarly, the failure of an intestinal anastomosis is likely to lead to an increased chance of death in hospital (eg of 1637 patients without anastomotic leak the mortality was 4%, which compares very favourably with the 19% mortality seen in the 196 patients whose anastomosis did leak). It has already been shown that there is a wide variation in clinical anastomotic leak rate between surgeons (range of 0.5% to 30%) so once again there are possibilities of large improvements in outcome by more attention to clinical surgery.

Turning to local recurrence, there are some surgeons who have low rates and some who have much higher rates, even when differences in case mix have ben taken into account. Indeed, one surgeon has reported a series of 115 cases of rectal cancer operation with local recurrence developing in only 3 of them . This achievement seems to have been brought about through specialisation, much in the same way that cardiac surgery has become increasingly safe with increasing specialisation.

Conclusion

Despite many great hopes, there is nothing yet in modern science and therapeutics that can have as great an impact on patient's well being after colorectal cancer surgery as: the general condition of the presenting patient; careful preoperative preparation; and the skill of the surgeon in the operating theatre.

IS FOLLOW-UP WORTHWHILE?

Mr Geoffrey Oates, The General Hospital, Birmingham

Some authors have argued that routine follow-up is of little value in tracing curable recurrences, whilst others have produced figures to show that as many as 20% of patients with recurrent disease detected at an early stage can have their survival prolonged by 5 or more years.

Few would quarrel with the argument that inadequate follow-up is a waste of time and resources, and perhaps even worse, it may provide a false sense of security to the patient and the clinician. A prime example of non-dedicated follow-up is the report of Cochrane and his colleagues from the Middlesex Hospital in 1980. 180 cases, of curative resection were quoted: of the 71 patients developing recurrent diseases, 41 (58%) were diagnosed at times other than the routine out patient follow-up appointments, and only 1 patient was believed to have been cured by further surgery. There was no set pattern of investigations, tumour marker studies were not used, (CEA was not available over much of the period in question) and the authors admit that "examination was often performed by a junior member of the surgical team, usually without sigmoidoscopy, barium enema or occult blood testing". This is NOT follow-up in my understanding, and contrasts sharply with that of Sugarbarker et al. Who appear to have gone to the other extreme in a prospective study with monthly CEA assay for 3 years, then at 3 monthly intervals for 2 or more years, with a clinical review which included a CT scan and chest X-ray every 4 months. Studying a small group of 66 patients at high risk of

recurrence, they concluded that the optimal follow-up plan was a simplified programme which included frequent CEA assays, clinical reviews, and surveillance of the remaining large bowel by colonoscopy.

What are the aims of follow-up in colorectal cancer patients?

1 Diagnosis of overlooked synchronous neoplasms

2 Detection of recurrent cancer

3 Detection of metachronous tumours

4 Support for the patients

5 Audit of results of treatment

6 To enable further curative or palliative treatment to be instituted at the earliest possible time

I shall endeavour to examine each of these points.

1 Synchronous tumours It is widely acknowledged that there is a 'miss rate' for synchronous tumours at the time of initial surgery for the obvious major pathology. It is accepted philosophy that the entire large bowel should be examined pre-operatively, by total colonoscopy, or less satisfactorily by double contrast barium enema. This is not always feasible with obstructing tumours of the left colon, and here the rule is that colonoscopy should be done within 3-6 months of operation. This is of particular importance if there are additional polyps noted with the original tumour. The general rule is that any second tumour found within 2 years of the first operations is a missed synchronous lesion. This is an aspect of follow-up - and in my opinion a mandatory responsibility.

2 Recurrent cancer The highest incidence of recurrent cancer occurs within the first 2 years, and hence the usual plan of more frequent review over this early stage. Many clinicians do not accept that further treatment is rarely possible. A prime example is in the meticulous follow-up required when an apparently early rectal cancer has been treated by local excision. Prompt detection of recurrent disease allows a 'second bite' in the form of radical excision. If the patient is left to present only when there are symptoms, it will always be too late.

I shall discuss the question of CEA-prompted second-look treatment. There is much evidence on this already, but we await the outcome of our own CRC Trial. The results of this are quite properly NOT being looked at on an interim basis. The use of CEA in this way introduces the important issue of lead time. When would recurrence have been detected if no CEA assays were performed? Boey et al. estimated this to be 41/2 months. Carlsson et al. calculated lead time provided by CEA to be near 6 months.

The widely differing success rates in detecting treatable recurrences will be considered, together with the importance of lack of delay between detection and treatment.

3 Metachronous tumours This is the area where there is least controversy. There appears to be a constant incidence of metachronous carcinoma with time. The rate varies in reported series up to 9%. A recent report from Denmark however, demonstrates a striking cumulative risk of 30% following 40 years of follow-up on a series of 501 patients who had curative surgery for an initial carcinoma when less than 40 years of age. The cumulative survival rate after operation

for a metachronous carcinoma was 41% after 20 years of observation. It was not difficult for these authors to advocate a life-long follow-up programme in this age group!

These studies do not include the prevention of metachronous tumours by the eliminations of non-malignant polyps in the remaining large bowel which is being studied by triennial colonoscopy.

4 The patient Whilst it may be desirable for the surveillance and support of patients to rest with the General Practitioner, the fact is that such provision is more than often lacking in the primary care sector. Moreover, the General Practitioner does not have the facilities for sigmoidoscopy, colonoscopy and CT scanning, though he/she could have access to regular CEA tests. Patients who have had surgery of the magnitude involved in the treatment of colorectal cancer require knowledgeable follow-up and support which can only be provided by the surgeon who knows exactly what was done and what is being done. The support aspect applies especially to patients with colostomies, (though it can be argued that these are better cared for in a separate stoma clinic), but patients with very low sphincter-saving resections also have problems with increased stool frequency and episodic incontinence, and help is just as necessary here. This is not a field where the average General Practitioner does well.

5 Audit This may be the most important aspect of follow-up. Without accurate data, how are we to know how well or how badly we are caring for our patients? How are we to discover changing epidemiology? The current underfunding of the Health Service extends even more severely

to Cancer Registries where follow-up data have been collated in the past. We have heard during this meeting of the immense variations in the results of individual surgeons, and if the achievements of the best are to have any influence on the not-so-good then appropriate follow-up statistics must be available from both groups. Follow-up in this respect is all too increasingly left to the enthusiasts who now have to find their own supporting funding.

6 Further treatment The potential for this must always be available if there is to be any point in searching for early recurrent disease. Provision must include highly skilled surgery, embracing radical second-time abdomino-pelvic exploration, major liver resections and lung resections. At a meeting last year of the Society of University Colon and Rectal Surgeons a poll revealed that less than 50% of those present were prepared to resect even favourable liver metastases, and yet there are published series showing that 30-50% further 5 year disease-free intervals are feasible in these patients with hepatic secondaries amenable to surgery. Similar figures are achievable with isolated pulmonary metastases.

THE USE OF OUTCOME MEASURES IN CANCER OF THE COLON AND RECTUM

Sam Ahmedzai, The Leicestershire Hospice

Biological outcomes of cancer

It is customary for medical students to be taught, when considering the natural history of diseases, to think in terms of symptoms, signs, investigations and treatment. Practising clinicians find it easy to be dominated by the latter two areas. The patient's presenting symptoms are recorded in the case-sheets, new symptoms are duly added but tend to be acted on only if they are thought to be 'relevant' to the main condition. Similarly, physical signs and other clinical findings are often 'filtered' and again only those which are considered relevant are followed up. For many busy doctors in surgeries, follow-up clinics and hospital wards the main subjects of interest are: what tests to do, and what to prescribe?

From the patient's point of view, living with a disease is not just a matter of morbidity and mortality. It is not always easy for a patient with cancer of the bowel to discern what is a symptom of the underlying disease, or of a side-effect of a treatment (surgery, radiotherapy, chemotherapy, pain killers etc), or of another condition altogether (stress ulcer, co-existing piles). It is always too easy for the patients to assume that any symptom, especially if it occurs 'somewhere inside', means advancing cancer and certain doom.

There is another view of disease, that of the family's experience. Cancer rarely affects just one person in a household: very commonly the 'ripples' are felt far beyond the immediate circle of relations, and into the wider network of informal carers, friends and colleagues at work.

The physical or psychosocial implications of colorectal cancer do not fit comfortably into the classic medical model of symptoms, signs, tests and treatment. The social and financial embarrassment which is added to these sequelae adds up to a very broad front of distress, which requires a broad-minded approach for their understanding and alleviation.

What are the measurable outcomes of disease?

It is of course essential to measure the 'hard' or totally objective variables in monitoring the progress of cancer. There are unfortunately not many of these: length of survival, size of tumour, and a few biochemical or haematological markers. They are mostly helpful for documenting recurrence, or progress of disease, but they correlate poorly with the patient's total experience. Looking critically at length of survival, even this begins to lose its 'objective' value when the patient's burden of disease (or his/her psychological reaction to the perceived burden) is even superficially considered. Attempts have been made to incorporate this into objective follow-up: 'symptom-free' survival, or 'time without symptoms' (twist) are increasingly quoted.

To these 'hard' data, oncologists commonly add an estimate of the patients' 'performance' - this refers to gross physical functioning and predominantly reflects the crude medical view of patients as either sick and dependent, or able to work. The application of performance status scales has been largely restricted to pre-treatment work-ups since they are well known to have prognostic significance at the time of diagnosis.

Whilst many doctors do not count symptoms as 'objects' for measurement, there is a wealth of evidence that they can be not only standardised, but also quantified in a reliable and valid way. There are two common approaches to symptom evaluation: linear analogue scale and verbal rating scale. It appears that the latter is gaining more ground in Europe and North America. Both have been shown to be reliable and repeatable. There are also two ways of applying the measurement: observer-rated (usually by doctor, nurse or other clinic staff) and patient self-rated. (A third way, of using a proxy rater such as a relative, is sometimes used but adds another dimension of potential bias). The patient self-rated method is conceptually more appealing and if critically interpreted, could potentially be most cost-effective.

The reduction of 'feelings' into numbers or grades of severity on a verbal scale is becoming well-established in many branches of medicine and nursing. Psychiatrists, psychologists and sociologists will point out that for many years they have used the same methods for quantifying psychological and social distress. Indeed the validation of psychosocial scales is far superior to the more recent 'medical' measures. Newer areas of formal study include the sexual

life of patients following disease and surgery; socioeconomic consequences; satisfaction with treatment. It is customary to consider these outcomes, together with physical symptoms, under the heading of 'quality of life'.

A problematic area in quality of life research is whether to concentrate on specific dimensions, as detailed above, or to take a broader look at 'global' well-being. The latter tells the clinician less about individual patients' experience, but helps the health manager to make wider comparisons with other diseases and treatments. Performance status scales, 'quality-adjusted life years' (QALYs) and 'health profiles' are examples of the global approach.

What sort of research has been done on outcomes?

Most qualitative research on the outcome of malignancy has focussed on breast and lung cancer. It is interesting to speculate that in both these diseases the motivation to study 'quality of life' may have been to justify giving more aggressive chemotherapy regimes - or to avoid doing so, depending on the attitude of the researchers. Studies on the subjective outcome of surgical intervention are less common, but again in breast cancer there has been interest in comparing the psychosocial effects of mastectomy versus breast-conserving operations.

In colorectal cancer there have been few published studies of subjective outcome of randomised interventions. Those which have considered qualitative issues, eg after surgery or laser treatment, have tended to be small trials and not controlled. Even so,

statistically 'significant' differences have been obtained. The interpretation of the results as biologically desirable outcomes is not easy.

The inevitable biological outcome for most patients with this disease is death. Again, so far few studies have been reported on the issues related to terminal illness from colorectal cancer. The increased input of palliative care services (not necessarily based in a hospice) has opened up more opportunities for research into the patient's and family's experience of advanced disease.

What are the priorities for future research?

It is important that future studies in colorectal cancer are large-scale and controlled. It would be wrong to simplify outcome measurement to purely 'objective' variables; or to confuse indicators of 'process' in health care with those of true clinical outcome.

The choice of subjective outcome measure needs to be carefully thought out in relation to the stage of disease, method of treatment, expected side-effects and cost-benefit issues. Evaluation methods should be validated and standardised for this population. For economic reasons it is helpful if the methodology could allow for comparisons with the management of other diseases.

Since many patients are unable to be 'cured' by present interventions, the outcome of 'active' versus more conservative 'wait-and-see' palliative management needs to be assessed by means of formal randomised trials. Alternatively, a consumer-oriented

approach to assessing satisfaction with care could be adopted. The ethical issues inherent in these studies will be challenging.

As hospice services make more inroads into community care and hospital departments, the allocation of their not inconsiderable cost towards the management of advanced disease needs to be evaluated. The role of specialist staff such as stoma care nurses should similarly be subject to audit.

Finally, with the opening of boundaries in Europe, there is a new challenge: the research into cross-cultural issues of patients' and clinicians' attitudes to cancer and its treatments.

THE PERSON WITH A STOMA

By Celia Myers, Clinical Nurse Specialist

Stoma Care Department, St Mark's Hospital

The patient about to undergo stoma surgery for colorectal cancer needs crucial and sensitive handling, so with this in mind, I will use a conceptual framework for my talk addressing the place the patient will occupy ultimately in society.

Working through the framework - initially exploring how the patient feels, his/her fears, anxieties and questions, gradually moving onto discuss family issues and relationships. An example is the middle-aged patient with a stoma having to adapt his/her lifestyle and work to having a stoma.

There are other issues; the patient's sexuality and accompanying fears of rejection and impotence, the feeling that a stoma is a threat to their relationship.

Some groups may have particular problems. Rectal excision is particularly distressing to a homosexual and the devastating curtailment of their sexual activities.

For certain ethnic groups it may be necessary to ensure the stoma is sited high - and to help the fears of rejection by the family.

If the patient cannot self care, due to advanced disease or the disabilities of old-age. Care may be transferred to a relative or friend or maybe even an old peoples home or hospice. Good support and liaison must be offered.

Lastly - how does society view the patient with a stoma. Does society see the patient as handicapped? Is the label of disability a further added complication to employment fears adding to anxiety in the work place and in society?