The Epidemiology of Alimentary Diseases

John M. Duggan and Anne E. Duggan

Springer

THE EPIDEMIOLOGY OF ALIMENTARY DISEASES

The Epidemiology of Alimentary Diseases

by

JOHN M. DUGGAN
University of Newcastle, Australia

and

ANNE E. DUGGAN
John Hunter Hospital,
Newcastle, Australia

Springer

A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN-10 1-4020-3839-9 (HB)
ISBN-13 978-1-4020-3839-6 (HB)
ISBN-10 1-4020-3840-2 (e-book)
ISBN-13 978-1-4020-3840-2 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

www.springeronline.com

Printed on acid-free paper

Printed in the Netherlands.

Dedication

This book is dedicated to
M.C.D who ultimately made all
this possible.

J.M.D

A.E.D

Contents

Contributing Authors

J.M. Duggan AM
M.D., B.S.(Hons), FRCP, FRACP, FRACMA
Conjoint Professor, School of Medical Practice and Population Health, Faculty of Health, University of Newcastle, Australia.

A.E. Duggan
B.A.(Hons), Dip. Ed., B. Med., M.H.P., Ph.D., FRACP
Conjoint Associate Professor, School of Medical Practice and Population Health, Faculty of Health, University of Newcastle, Australia.

Preface

In offering this book to what we hope will be interested readers, we have several aspirations. We have aspired to present to students and clinicians a rather narrow view of epidemiology concentrating on the causal factors and setting of the more usual gastroenterological problems and giving greater space to conditions of importance for which major knowledge of causation and course is available. Part of the rationale is the belief that modern medicine lays excessive emphasis on therapy with increasingly expensive, and in many cases, dangerous drugs and too little emphasis on the causes and avoidance of disease. We are of the view that traditional views handed down through generations of clinicians need scrutiny worthy of 21st century medicine whose currency includes topics like nanomoles, megabytes and logistic regression. We hope that clinicians will see that there is often a practical application to the findings of epidemiological exploration and that what passes for canonical knowledge is so often unsubstantiated myth and are fully aware of the reluctance of organized medicine to reject old paradigms in favor of the new, matched by an often uncritical enthusiasm for new therapies.

Our researches have increased our belief in the major role of social factors especially diet, both in quantity and quality in many disorders and that clinicians have a responsibility to provide appropriate advice to policy makers as well as patients.

Aware of effect of exposure of undergraduates to the social determinants of disease on their post graduate modes of thinking, we hope that some will even seek to extend their horizons of medicine.

It has been decided that a critical examination of the results of intervention, a part of the landscape of clinical epidemiology is not within

our mandate although it clearly is a field already receiving the deep ploughing it warrants.

Thomas Chalmers, later President of the American Gastroenterological association, in an editorial in Gastroenterology as far back as 1964 made a plea for greater integration of clinical and scientific medicine, quoting Franklin White from a century ago "the new therapy has reduced mortality sharply, but the number of funerals seems to have remained the same". His conclusion was that if clinicians were willing to test hypotheses properly, the funeral rate would drop with the mortality rate (1).

To the public health worker and health policy bureaucrats we offer what we hope will be some evidence to catalyze what must be their frustrating task of trying to bring their expertise into mainstream medicine.

In showing a little of the historical background of some present concepts, maybe we have helped develop interest in what may be conceived as an uninteresting aspect of medicine. If a John Snow should emerge from one of our readers then our efforts will have been fully justified.

JMD

AED

Reference

1. Chalmers TC. Editorial. Mortality rate versus funeral rate in clinical medicine. *Gastroenterology* 46,788-791 (1964).

Foreword

The thought that led to this book began in John Duggan's work for the Repatriation Medical Authority in Australia. That Authority produces Statements of Principle which form causation templates for war veterans' compensation claims in Australia. These templates provide a definition and list of contributory causes for all diseases based on the current epidemiological literature. They are legally binding on all decision makers in veteran's compensation and are made at two standards of proof (i.e. Reasonable Hypothesis and Balance of Probabilities), which apply on the one hand to active war service and the other to non-warlike service. The need to meet the rigours of producing a legal document and the social purpose of providing generous compensation terms to war veterans produced an environment in which the five academic members of the Authority had to view the epidemiology in a fresh light. The multiple interactions of many factors responsible for all diseases became highly relevant to compensation claims. The need to make judgements at two different standards of proof on the same body of evidence focused attention on both the quality of evidence and the whole body of evidence and the process of scientific decision making itself. John Duggan's experience, wisdom and good humour were much appreciated in this process and will infiltrate this book to the readers' pleasure.

Professor Ken Donald
Head, School of Medicine
University of Queensland
Brisbane, Australia

Acknowledgments

This book would not have seen the light of day without the stimulus and assistance of many talented people. It had its genesis in the meetings of the Repatriation Medical Authority, a body set up by the Australian Parliament to determine the causative factors for disease based upon "medico-scientific principles" for the determination of pensions for Australian ex-service personnel for disability attributable to armed forces service. Over the eight years one of us (JMD) served on the Authority it became evident that determining the causation of a condition requires detailed and exhaustive literature review followed by critical expert analysis of the data. It was clear that the standard textbooks were often not only inadequate but sometimes lacked scientific credibility. For most organ systems, no such single source of information existed. So arose the concept of a book on the subject. To the Chairman, Professor Ken Donald and the members, Professor Dick Heller, now Professor of Public Health in the School of Epidemiology and Health Sciences in the University of Manchester England, Professor Beverley Raphael, Professor John Kearsley and Professor John Kaldor and the very talented secretariat staff, especially its leader, Dr Alex Bordujenko for their knowledge of epidemiology and their diligent support we are grateful. To Professor Heller, with his profound knowledge of epidemiology and incisive approach to problems much is due.

Mrs Patricia Aguado, Chief Librarian of the Gardiner Library at the John Hunter Hospital and her staff opened many doors to ferret out obscure references, forever cheerfully. Mrs Mary Howard also of the library staff provided the indexing.

Our secretaries, Mrs Amber Charman and Mrs Allison Colyvas typed numerous drafts skilfully and with equanimity. We are both aware of the

debt we owe to those of our own teachers who taught us to question dogma and tried to inculcate a spirit of enquiry in us. We are reminded of a possibly apocryphal story of graffiti outside a University Philosophy Department – "Question everything" under which someone had scrawled "Why?".

JM Duggan
AE Duggan

Chapter 1

EPIDEMIOLOGY AND CLINICAL PRACTICE

Epidemiology may be defined as "the study of the distribution of a disease or a physiological condition in human populations and of the factors that influence this distribution" (1). The term, however defined, refers in principle to determining factors which influence disease processes in humans. Although often associated with causes it may also concern itself with factors which diminish disease such as dietary folate and colorectal cancer, fluoride and dental caries, coffee and diabetes, exercise and ischaemic heart disease. The epidemiology of diseases is not a topic that makes most clinician's eyes light up. Equally, progressively medical schools are emphasising the social milieu in which illnesses present (2). In many respects, the sociological aspects of illness represent a low power view of the environmental influences so potent in health and its disorders – diet, water quality, social class, employment, housing, income, education, occupational hazards. We believe that epidemiology has a role and can be interesting to students and practitioners at the bedside just as it is relevant to more senior clinicians. One of us is old enough to recall when bronchogenic carcinoma was recognised as developing epidemic status when no-one seemed to have noticed the nicotine stains on the patient's fingers.

The definition given has two words worth emphasis. Firstly, we are concerned with "humans" which distinguishes it from animal research, although there must surely be a corresponding discipline for animal workers of which the complex story of the sheep industry in Australia provides an example. The second word to emphasise is "population". Epidemiology is not concerned with the individual as in standard clinical practice but with the health of the group. This takes us to two aspects of epidemiological work:-

1. Examination of the distribution of disease frequency in the population. This can produce hypotheses about the findings of the work. This is then a descriptive study.

2. Analytical studies which test the hypotheses generated by the descriptive studies.

1. DESCRIPTIVE STUDIES

These use population based statistics on disease incidence, morbidity, mortality, hospital and health data; anything dealing with disease or disability in the population.

2. ANALYTIC EPIDEMIOLOGY

This utilises data on patient characteristics, residence, occupation, lifestyle, leisure activity, diet, medication, the whole gamut sometimes of human existence. Such data are used to seek relationships between health statistics and population factors testing hypotheses of linkage and causation.

A characteristic so often seen in applying epidemiological data to clinical situations is the entrenched conservatism of practitioners and populations in respect of the utilisation of the findings. There are two outstanding examples which have quite significant historical importance, apart from their medical significance. In 1535 Jacques Cartier rediscovered Newfoundland and, as was usual, his crew was devastated by scurvy. Hakluyt in his "Principal Navigators" in 1600 described how a decoction of a local tree, probably the spruce fir, as advised by the local Iroquois Indians, provided a rapid cure. Yet the conventional wisdom could not accept a nutritional cause for the disease. James Lind in 1747 took 12 identical cases of the scurvy and gave each pair a purported remedy. Only the pair given two oranges and one lemon a day dramatically recovered. Published in 1753, it was ignored until James Cook utilised this knowledge for the triple circumnavigation of the globe and provided preserved cabbage throughout the voyage for his crew. He was the first navigator to escape scurvy and to discover eastern Australia and much else of the then unknown world and altered the course of history. Yet, only after 42 years could the Lords of the Admiralty be induced to prescribe a source of vitamin C for British sailors. Doubling the effective strength of the Royal Navy, this played a major role in Britain's defeat of the French navy in the Napoleonic wars.

Another example is of cholera which, present in Bengal for centuries, migrated to Europe and reached England early in the 19th Century causing 5500 deaths. It struck Sunderland in 1831 where a young medical apprentice, John Snow, observed the disease then attacking the coal miners particularly. He rejected the current paradigm of a 'miasma' or bad air as

the cause and concluded that diarrhoea with faecal contamination, particularly in coal mines, unwashed hands and shared food was causative. By 1848 he was a well regarded general practitioner in London when an explosive outbreak occurred. Snow, recalling his earlier experience still thought that the disease was spread by faecal contamination of water. He found that 73 of the 83 deaths in three days were in people living near and using the Broad Street pump. Eight of the other ten occasionally used the pump. After a prolonged debate he convinced the Board of Guardians of the local parish to remove the handle from the Broad Street pump. They did. The epidemic ceased. Thirteen years later, although he had achieved sufficient status to anaesthetise Queen Victoria for the birth of her last child, his discoveries had failed to achieve recognition leading to a tragic irony. The Queen's residence, Windsor Castle, still drew its water from the Thames into which it also emptied its sewage, leading to Albert the Prince Consort acquiring typhoid fever from which he died.

Both these examples of what could be called Public Health in action can be regarded as Applied Epidemiology. However, both illustrate two poorly appreciated aspects of the process. Firstly, those who like Lind and Snow, produce a new paradigm may have to face the apathy of the conservative medical and civil authorities (3). Secondly, epidemiological observations when put appropriately into practice may have major and lasting repercussions.

We may consider some aspects of the quality and type of evidence that epidemiological studies produce. *The US preventive services taskforce : Guidelines for Evidence* are valuable and provide a hierarchy to evaluate the quality of study design, 1 being the best and 5 the least potent.

3. ANALYTIC STUDIES

1. Intervention Studies
   - 1a. Randomised Controlled Trial
   - 1b. Controlled Trial
2. Observational Studies
   - 2a. Cohort-Prospective
   - 2b. Cohort-Retrospective
3. Case Control Descriptive Studies
4. Population (Correlation)
5. Individual
   - 5a. Cross Sectional Surveys
   - 5b. Case Series
   - 5c. Case Reports

We are influenced by these but a major influence in our evaluation is the Bradford Hill criteria (4).

1. Strength of Association
2. Consistency
3. Specificity
4. Temporality
5. Biological Gradient
6. Plausibility
7. Coherence
8. Experimental Evidence
9. Analogy

Such criteria are an essential tool in evaluating epidemiological evidence in a field so fraught with associations, bias effects masquerading as causes. To those who believe that epidemiology is an esoteric subject, largely residing in the computers of academics who have never seen a real patient for years, we extend our sympathies and particularly to their patients. Too often we have seen patients with Crohn's disease whose physicians have not realised that smoking is impairing the patient's response to their ready administration of potent but dangerous drugs.

One of the major influences in the rise of epidemiology and particularly analytical epidemiology has been the fantastic growth of computing capacity in the last several decades. In one of the key books of an earlier era, J N Morris' *Uses of Epidemiology* (1964) neither logistic regression nor meta analysis appear.

We have interpreted our role as one to bring to clinicians and to those concerned with health promotion an account of the current knowledge of the factors concerned with the development of disease, with some emphasis on the critical interpretation of the relevant literature. We have also tried to highlight some of the gaps in knowledge; if this stimulates young minds to attempt to fill those gaps, our joy will be unbounded. In a sense we are promoting Evidence Based Medicine, not in patient management, but in population management, with better management of the individual patient an important by-product. For example, if smoking is accepted as a significant promoter of peptic ulcer and Crohn's disease, then the clinician has a responsibility to promote smoking cessation as part of a patient's management plan, meanwhile supporting Public Health endeavours to reduce smoking in the community.

References

1 Lilienfield A M. *Foundations of Epidemiology*. (OUP, New York, 1976).
2 Susser M W, Watson W. *Sociology in Medicine*. 2nd Edn. (OUP, London, 1971).
3 Kuhn T S. *The Structure of Scientific Revolutions*. 2nd Edn (University of Chicago Press, Chicago, 1970).

4 Bradford Hill A. The Environment and Disease: Association or Causation. *Proc. Royal Soc. Med.* **58**, 295-300 (1965).

Chapter 2

SOME EPIDEMIOLOGICAL CONCEPTS

As we discussed in the previous chapter, epidemiology is the study of the distribution and determinants of disease frequency in human populations. To do this effectively we need some mechanisms to count events of interest and to observe populations.

These methods need to be applied to the two main approaches to epidemiology:

1. Descriptive studies: Studies that examine the distribution of disease frequency in populations to develop a hypothesis as to the cause of the disease, and
2. Analytical studies: Studies that test these hypotheses by reviewing personal characteristics of patients observed or, exposure to items of interest among individuals within the groups observed.

Descriptive studies use population-based statistics of disease occurrence, survival and mortality. Disease registers often provide important information. Two important concepts are:

Incidence - the number of new cases during a given period of time divided by total population at risk and

Prevalence - the number of existing cases of a disease divided by the total population.

Measures of exposure are often broad and subject to confounding or interfering factors. Before we conclude any associations between a disease and its possible determinant it is important to consider any factors that may influence study results.

Analytic studies are either observational or interventional. Clinical medicine relies heavily on interventional studies often in a randomized format to assess the value of proposed new interventions.

For the epidemiologist analytic studies are the bread and butter of epidemiology with two valuable study designs: case control studies and

cohort studies. Case control studies select subjects on the basis of whether they do (cases) or don not (controls) have a particular disease. The groups are then compared for the proportion having a history of exposure or characteristic of interest. A classic example is whether lung cancer patients have a more significant history of smoking than non lung cancer patients. Case control studies have a number of advantages. They are particularly suited to studying rare diseases because they allow the investigator to collect together an adequate sample size. They allow multiple exposures to be assessed and in the early stages of our knowledge of a disease may come up with some interesting surprise associations!

Subjects in cohort studies are classified according to their exposure to a particular factor (exposed or unexposed) and then followed for a specific period of time to determine the development of disease in the exposed group. As is easily imagined this can be years. The Nurses Health Study continues to be an important source of data having enrolled 120,000 female nurses in 1976. Second yearly these nurses complete an extensive questionnaire about a number of demographic, lifestyle aspects of interest and their medical history. This has allowed the investigators to identify important associations between lifestyle factors and diseases such as high blood pressure and a variety of cancers.

1. EVALUATING CAUSE AND EFFECT RELATIONSHIPS

Making judgements about causality from epidemiological data involves a change of logic that addresses two major areas:

a) Whether the observed association between an exposure and the disease is valid.

b) Whether the evidence provided from all the sources available support a judgement of causality.

Let us consider each of these issues in turn.

2. IS THE ASSOCIATION BETWEEN EXPOSURE AND DISEASE VALID?

There are three common explanations for why this might not be the case:

- Chance
- Bias
- Confounding

2.1 Chance

One can imagine that the smaller the sample size the greater the variability in estimates. Not surprisingly, one way to reduce the risk of chance is a large sample size. This reduces variability and provides more reliability of any inference made about the data. One important method for coping with variability in studies is to use confidence intervals (CI). Confidence intervals take into account the sample size and the expected degree of variability and provide a range within which the total magnitude of effect is likely to fall. A 95% confidence interval is commonly used and indicates with a 95% confidence that the true value of the variable (e.g. mean) lies within the interval. In contrast the p value, a composite measure of the magnitude of the difference between the groups and the sample size is susceptible to these factors and so a true difference may not be detected with a small sample size and visa versa. By convention if the P value is used then if it is less than or equal to 0.05, meaning that there is no more than a 5% chance of an observed result being due to chance, the association between exposure and disease is considered significant.

2.2 Bias

Bias is anything or process that deviates the results from the truth. This can occur by the way we select patients, observe them or question them and influence the way they respond.

2.3 Confounding

Confounding comes from the Latin to mix together and refers to failure to separate the effects of two processes. A confounder must be associated with the exposure of interest and independent of the exposure be a risk factor for the disease. An example of confounding is to conclude that a vegetarian diet reduces risk of cancer when it may also be that vegetarians also do a number of activities that also reduce cancer risk such as exercise.

3. GENERALISABILITY

Generalisability is another important question to consider when reading the results of epidemiological studies, that is: Do these results apply to the population in general or the population I am dealing with? Obvious

examples where there may be no generalisability would apply in results of studies of men to women or of one culture to another.

4. JUDGEMENT OF A CAUSE – EFFECT RELATIONSHIP

Simply because there is a valid statistical association between factors does not imply any causality between the two factors. It may simply be due to chance! As discussed in the previous chapter, in epidemiology there are a number of criteria that can aid in the judgement concerning causality. It may be worth considering these factors more closely:

- Strength of the association. It should not be a surprise that the stronger the strength of an association the less likely it is due to chance, bias or confounding.
- Biologic credibility of the hypothesis. It is important to remember that a statistical association that does not appear credible at one point in time may eventually appear to be so once we understand mechanisms.
- Consistency of the findings. Put simply the more studies supporting a hypothesis the more like the hypothesis is correct.
- Temporal sequence. It is logical that the exposure of interest should precede the disease of interest but this may not always be easy to establish.
- Dose – response – relationship. The observation of a gradient of risk with the degree of exposure is always reassuring.

Quantifying any association between exposure and disease is an important epidemiological tool. Relative risk calculates the size of the association between exposure and disease and the likelihood of developing the disease in the exposed group. It is the ratio of the incidence of disease in the exposed group divided by the corresponding incidence of disease in the unexposed. A relative risk of 1 indicates that the incidence of disease is the same in both the exposed and unexposed group. In case control studies cases already have the disease and so one can only calculate the odds of exposure among cases and controls. For example people who smoke may be shown to have a higher risk of pancreatic cancer or some of the other gastrointestinal diseases we are about to encounter. When we use the odds ratio we often calculate the corresponding 95% confidence interval to give with 95% confidence the upper and lower limits of the risk. Thus if we could come up with the estimate of relative risk of myocardial infarction with use of the oral contraceptive pill as RR (95%CI)= 0.7 (0.5-1.2). As the estimate includes 1 that is an equal risk in the exposed and unexposed groups the association is unlikely to be significant.

A word needs to be said about Attributable Risk, a measure known to epidemiologists but only now coming into the clinical literature. A simple example will illustrated. Suppose that in a population the prevalence of smoking is low and the relative risk of smoking for lung cancer is low. Then, in that population, only a small proportion of cases of the disease can be attributed to smoking. Conversely, if the prevalence of smoking is high and the relative risk is high, then a much larger proportion of the disorder can be attributed to smoking.

Put mathematically

If r = relative risk of lung cancer in smokers compared to non smokers and,

b = background prevalence of smoking in that population,

then Attributable Risk (AR) = b (r-1)/b(r-1)+1.

AR can be expressed as a percentage by multiplying by 100. It may be made to deal with multiple factors; standard errors and confident intervals can also be calculated. It also needs to be noted that as originally defined it is the "maximum proportion of lung cancers attributable to cigarette smoking". (See Lilienfeld, *Foundations of Epidemiology* NY, OUP.,1979).

Logistic regression is a very complex computational method of separating out the significance and strength to be attached to factors which may be contributing to an end result. If we consider various elements of diet, age, socio economic factors, duration in a condition like bowel cancer it can attack significance and strength to these factors.

Background Reading

Last J. *A Dictionary of Epidemiology.* 4th edn (OUP, Oxford, 2001).

Hennekens CH, Buring JE, (eds.) *Epidemiology in Medicine.* (Little, Brown and Co., Boston, 1987).

Chapter 3

GENETICS AND THE GUT

At first glance there appears to be little role for the epidemiological aspects of hereditary disorders, especially given that such disorders represent a minor part of the load of GI diseases in most communities. However, it will become evident, with modern techniques of genetic and molecular biology, that genetic factors play a significant role in the natural history of an increasing number of disorders. However, it must be recognised that, ultimately, all cancers have a genetic basis, with cancers representing the end product of complex interaction between environmental influences and specific genes of the subject. It is proposed to discuss a number of disorders that are important, both from their frequency, and mortality and our developing knowledge of their genetic background. For those seeking more detailed information, large genetic texts are necessary (1).

1. INFLAMMATORY BOWEL DISEASE

This consists of two similar but distinct entities, ulcerative colitis (UC) and Crohn's disease (CD), both frequent, important in terms of morbidity and mortality and for which genetic and environmental factors are intertwined in causation. The clinical factors are considered elsewhere; here we will emphasise the genetic aspects.

1.1 Racial and Ethnic Influences

For several decades it has been recognised that these are major influences; IBD was more frequent in Jews of Ashkenazi origin than in their fellow Americans, there was a marked north / south gradient in Europe and Caucasians had a higher incidence than non-Caucasians of both CD and UC

and in the U.S. there were higher rates in whites than blacks and Hispanics with Asians lower still. It is also evident that there is a strong familial tendency in both diseases with a 10-30 fold increase in the rate in siblings of patients. UC is increased in relatives of UC patients and CD in relatives of CD patients but CD and UC may co-exist in families more often than dictated by chance. It is also evident that familial aspects are stronger in CD (25%) than in UC (17%). In southern Israel IBD is nine times more prevalent in Jews than in non Jews. Whilst these differences may be attributed to environmental influences, several observations indicate a genetic basis; an increased prevalence in twins, absence of spouse concordance and concurrent disease in relatives widely separated geographically. Nonetheless, a straight Mendelian inheritance is excluded on the basis of these observations. Equally, detailed analysis excludes the proposal of a polygenic model where those with 10-15 specific genes develop CD, those with fewer develop UC and those with relatively only few of these genes develop UC rather than CD. The latest data indicate that the genetic basis for IBD is in the interaction of two or more major genes with genetic heterogeneity for UC and CD. This leads to the conclusion that IBD is a heterogeneous group of diseases with each subform an oligogenic disease due primarily to the interaction to a limited number of genes with or without a minor contribution from modifying genes (2).

As indicated elsewhere there are a number of epidemiological factors that influence the development of IBD such as smoking, diet, the oral contraceptive pill and appendicectomy. So these disorders have both genetic and environmental causes. A novel explanation for the relatively high frequency of the susceptibility alleles with their major roles in morbidity and mortality has been presented (3). A simple explanation is that they are due to mutations. However, their high morbidity and mortality would necessitate a very high mutation rate to compensate for the loss of life and reproductive capacity from them, one much higher than the estimated $1/10^5$ to $1/10^6$ rate per gene locus in humans.

Another explanation, the founder effect is also excluded. This concept is that a mutation occurs in an individual and is handed down to a high percentage of the descendants. While applicable to isolated communities and certain ethnic groups, it is invalid for IBD with its high frequency and wide distribution. The remaining explanation is best, namely that carriage of the IBD gene also carries a selective advantage. Examples of this in gastroenterology already exist; the protection against cardiovascular disease and hypertension in DU and the protection against iron deficiency given by haemochromatosis. The concept is that the possession of a disease producing gene and a benefit ultimately leads to an equilibrium between benefit and ill effect. In a case of IBD, the presence of the IBD genes

provides immunoprotection to the young in an unsanitary world. However in a sanitary world, the protective influences remain armed to protect the individual leading to hyperstimulation on contact with an infectious agent and also to the primed state leading to dysregulation of the protective processes and an autoimmune state. For the Ashkenazi Jews of central Europe living in crowded ghettoes in unsanitary conditions for centuries, the protective genes become a liability in our sanitised world. (4) The specific gene loci are referred to in the Crohn's disease chapter.

2. GUT NEOPLASIA

Although neoplasms of the gut are the most frequent neoplasms in any organ system in humans, the vast majority appear to be caused by environmental factors interacting with host factors and how the host factors respond to the environment. Only a minority have a major hereditary component. Of these, the principal ones are colorectal cancer; for oesophagus, stomach, pancreas, and liver, genetic influences are thought to be minimal and will not be discussed further.

Neoplasia related to genetic disorders is mainly seen in the colon in Familial Adenomatous Polyposis (FAP) or Gardner syndrome and in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome where the genetic effects swamp environmental factors (5). These two have been intensively investigated producing much information about tumourigenesis in general. It is thought that colon cancer arises by one of two main pathways – a stepwise succession of cellular events involving mutations in oncogenes and / or deletions of tumour suppressor genes leading to the familiar picture of premalignant and malignant colonic lesions.

3. ADENOMATOUS POLYPOSIS COLI (APC)

This gene on chromosome 5 functions as a tumour suppressor gene. Its protein product is β catenin which is intimately involved in cellular proliferation. A mutation in the gene occurs in Familial Adenomatous Polyposes (FAP) and also in sporadic cancer and in around 60% of sporadic adenomas, so that successive mutations lead to cancer. Current thought is that tumour development occurs initially with a mutation in the APC gene with progression through a sequence of steps associated with mutations and represented by a sequence of morphological changes from normal through adenoma to a cancer.

4. FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

This is due to a mutation in the tumour suppressor gene APC on chromosome 5q. It is an autosomal dominant in which large numbers of adenomatous polyps occur in the colon, occasionally in the small bowel and rarely in the stomach (5). The polyps occur in the young and by age 16, have developed in 50% of subjects. Death supervenes from the transition to colon cancer with death at average of 42 years, the disease being due to the loss of both APC alleles in the adenoma. There is some evidence of environmental influences having a modifying effect on the phenotypic expression in FAP.

5. HEREDITARY NON POLYPOSIS COLORECTAL CANCER (HNPCC) OR LYNCH SYNDROME

This is an autosomal dominant disease associated with cancers, both colonic and at other sites. It is due to a germline mutation in one of the Mismatch Repair (MMR) genes and is characterised by microsatellite instability in the carrier. Cancer occurs mainly in the colon and to a lesser extent in the endometrium and at an earlier age, 40-54 years, and there is an increased risk of cancer in the stomach, small bowel, ovary, kidney, brain but not breast. It is not clear that environmental influences play a significant role. The syndrome probably represents about 6% of colorectal cancers.

References

1. Rimoin DL, Conner IM, Pyeritz RE, Korf BR, eds. *Emory and Rimoin's Principles and Practice of Medical Genetics*. 4th ed, (Churchill Livingstone, London, 2002), Vol. 2.
2. Rotter JI, Yang H, Taylor KD. Inflammatory bowel disease. In: Rimoin DL, Conner IM, Pyeritz RE, Korf BR, eds. *Emory and Rimoin's Principles and Practice of Medical Genetics* 4th ed. (Churchill Livingstone, London, 2002), Vol. 2.
3. Passarge E. Gastrointestinal tract and hepatobiliary duct system. In: Rimoin DL, Conner IM, Pyeritz RE, Korf BR, eds. *Emory and Rimoin's Principles and Practice of Medical Genetics* 4th ed. (Churchill Livingstone, London, 2002) Vol. 2.
4. Rotter JI. Inflammatory bowel disease (letter). *Lancet* **343**,1360 (1994).
5. Boland CR, Helzer SJ. Cancer of the colon and gastrointestinal tract. In: Rimoin DL, Conner IM, Pyeritz RE, Korf BR, eds. *Emory and Rimoin's Principles and Practice of Medical Genetics*. 4th ed. (Churchill Livingstone, London, 2002), Vol. 2.

Chapter 4a

REFLUX OESOPHAGITIS

1. DEFINITION

Reflux oesophagitis disease means the presence of regurgitation of gastric contents into the oesophagus with endoscopic or histological evidence of oesophageal inflammation with or without associated symptoms. It attracts ICD 10AM Code K21.

It is necessary here to make a number of distinctions:

- GASTRO-OESOPHAGEAL REFLUX DISEASE is an end result, clinical and pathological, of the reflux of gastroduodenal contents into the oesophagus.
- GASTRO-OESOPHAGEAL REFLUX is the movement of gastric contents into the oesophagus. Such a process is frequent in normal individuals and generally has no adverse consequences.
- REFLUX OESOPHAGITIS is a condition in which there are histological or even visual changes in the oesophagus, such as erosions, inflammation, ulceration as a result of reflux. There may be no symptoms.
- HEART BURN/DYSPEPSIA often takes the form of a lower retrosternal burning discomfort. It may be due to reflux oesophagitis which may also be symptomless. Heartburn/dyspepsia may also occur in the absence of endoscopic or histological changes in the oesophagus. Oesophagitis and dyspepsia may be regarded as independent variables.

2. PREVALENCE

This is extremely difficult to determine with any precision. We may consider:-

1. What is the prevalence of dyspepsia?
2. What is the prevalence of reflux disease in dyspeptics?
3. What is the prevalence of reflux disease in the symptom free?
4. What is the prevalence of dyspepsia in reflux disease?

1. The prevalence of dyspepsia is readily determined. Representative figures are 20-40% in Europe and 22% in the U.S. with slightly higher figures in females than males and in the young.

2. The prevalence of reflux disease in dyspeptics has been extensively studied and is about 10%. Strangely, in spite of much work on developing categories of dyspepsia symptoms and their significance, they are of little discriminant value in the nature of dyspepsia whether ulcerlike, dysmotilitylike, refluxlike or non-specific (1).

3. Reflux itself is both frequent and normal in the symptom free. However, reflux episodes are as a rule, brief, more likely after meals and occur during the day rather than during sleep. Reflux disease is not uncommon in the symptom free but the data are unclear.

4. The prevalence of dyspepsia in reflux disease leads to question of the prevalence of symptoms in those with reflux disease. Unfortunately, although it is widely held that reflux disease may be symptomless, good data on its prevalence have not been found.

3. PATHOGENESIS OF GASTRO-OESOPHAGEAL REFLUX

This is multifactorial. The principal factors protecting the oesophagus from reflux of gastric contents are:-

a. The lower oesophageal sphincter (LES),

b. The crura of the diaphragm which enclose the lower oesophagus,

c. The acute angulation of the oesophageal junction with the stomach producing a flap valve,

d. The anchored gastro-oesophageal junction (2). Oesophageal clearing is impaired in patients with hiatus hernia.

The lower sphincter is served by excitatory and inhibitory fibres. The excitatory impulses are mediated by acetyl choline; the inhibitory by vasoactive intestinal polypeptide (VIP) and nitric oxide. The tone of the LES is inhibited by fatty meals, belching, smoking and xanthine containing drinks, coffee, tea, cola. Numerous humoral factors influence the sphincter

tone. There is good evidence that the tone in the LES is lower in patients with gastro-oesophageal reflux disease than in controls. In a study of 184 patients with reflux disease who received extensive investigations including endoscopy, manometry and oesophageal pH monitoring, patients with oesophagitis had lower oesophageal sphincter pressures, more frequent reflux episodes and longer periods of acid contact with the oesophagus (2)

4. RISK FACTORS FOR REFLUX OESOPHAGITIS

There are numerous. The major ones are:- hiatus hernia, obesity, pregnancy, drugs, alcohol, tobacco, gastric distension, heredity, naso gastric intubation.

4.1 Hiatus Hernia

The evidence for an association is very strong. A number of studies have reported a prevalence of hiatus hernia of 50-94% in patients with gastro-oesophageal reflux disease, prevalence in controls around 13%. Those with reflux oesophagitis have a 16.5 fold increase in the prevalence of hiatus hernia (2). Conversely, oesophagitis is, at the most, uncommon in the absence of a hiatus hernia. Recent studies clearly indicate that the presence of a hiatus hernia is associated with significantly increased susceptibility to reflux by reducing sphincter pressure (3).

4.2 Obesity

Although widely regarded as associated with reflux, the data are sparse and conflicting. One detailed study of 55 massively obese patients found reflux symptoms in 73% especially in the older patients. On the other hand a study of 75 predominantly young and middle aged female candidates for obesity surgery found normal sphincter function. Clinical experience suggests a higher prevalence of reflux symptoms in obese middle aged women but good data on this are lacking. Essentially, objective changes in oesophageal function are confusing in obesity. It may be that dietary fat lowering LES pressure is the culprit (4).

4.3 Pregnancy

Symptomatic gastro-oesophageal reflux occurs in 30-50% of pregnant women. The mechanisms are debatable. It is not due to abnormal distension

and does not occur in males with ascites; it is most likely related to hormonal factors in pregnancy.

4.4 Anticholinergic drugs

These are widely held to predispose to gastro-oesophageal reflux disease. Other drugs are nitrates, beta-adrenergics, diazepam and aminophylline. The relation with NSAIDs is complex. Two associated series of patients with ulcerative oesophagitis matched with hospital and with community controls showed no association with NSAID use (5), but another large study found an OR of 2 (1.3-3.0) for use of NSAIDs in patients with oesophagitis (6). There is evidence from a very large VA study of an association of erosive oesophagitis and oesophageal stricture with painful arthritic conditions. The likelihood is that in those with reflux, NSAIDs produce ulceration and stricture by a local action. (7).

4.5 Alcohol

The effect of alcohol, even given IV has been widely studied. In essence, alcohol is associated with gastro-oesophageal reflux by the lowering of LES pressure and impaired oesophageal clearance.

4.6 Tobacco

That there is an association is clear; however, the data on mechanisms are conflicting. Smoking seems to be associated with an increased rate of reflux events and sphincteric pressures are probably lowered.

4.7 Gastric Distension

While it is clear that delayed gastric emptying is associated with reflux, the evidence is that while gastric distension produces reflux, it is not a factor in the usual patient with GER disease.

4.8 Heredity

It is now clear that there is a major hereditary factor in gastro-oesophageal reflux disease. The major evidence comes from a study of 8411 twin pairs over 55 years of age in the Swedish Twin Registry who underwent a detailed telephone interview for reflux disease symptoms. The data show an hereditability of 31% (0.23-0.38) for such symptoms (8).

4.9 Naso Gastric Intubation

Naso gastric intubation is associated with oesophageal reflux and oesophagitis. Although it is more often associated with prolonged e.g. weeks of intubation in the recumbent position and even stricture formation, it may occur within 72 hours (4).

In summary Gastro-oesophageal reflux disease is frequent in all western societies studied but the prevalence in the lesser developed world is less clear and may be lower. It complicates gastro-oesophageal reflux which is a normal phenomenon but less well developed in the adult population. Its pathogenesis is complex and multifactorial and is almost always associated with hiatus hernia. Although it is regarded as having characteristic symptoms, objective data indicate that its symptoms are often non specific.

References

1. Talley NJ, Weaver AL, Tesmer DL, Zinmeister AD. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscope. *Gastroenterology* 105,1378-86 (1993).
2. Sontag SJ, Schnell TG, Miller TQ et al. The importance of hiatus hernia in reflux oesophagitis compared with lower esophageal sphincter pressure on smoking. *J Clin Gastroenterol.* **13**,628-43 (1991).
3. Kahrilas PJ, Lin S, Chen J, Manka M. The effect of hiatus hernia on gastro-oesophageal function pressure. *Gut* **44**,476-87 (1999).
4. Horwhat JD, Wong RKH. Risk factors for gastoesophageal reflux disease. Types and mechanisms. In : Orlando RC ed. Gastroesophageal reflux disease. (Marcel Dekker , New York, 2000), pp. 27-83.
5. Ryan P, Hetzel DJ, Shearman DJ, McMichael A. Risk factors for ulcerative oesophagitis : a case control study. *J. Gastroenterol. Hepatol.* **10**,306-12 (1995).
6. Voutilainen M, Sipponen P, Macklin J-P, Juhola M, Farkkila M. Gastroesophageal reflux disease : Prevalence, clinical, endoscopic and histopathological findings in 1128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. *Digestion* **61**,6-13 (2000).
7. El-Serag HB, Sonnenberg A. Association of oesophagitis and oesophageal strictures with diseases treated with non-steroidal anti-inflammatory agents. *Am. J. Gastroenterol.* **92**,52-6 (1997).
8. Cameron AJ, Lagergren J, Henriksson, Nyren O, Lockett GR, Pedersen NI. Gastroesophageal reflux disease in monozygote and dizygote twins. Gastroenterology **122**,55-9 (2002).

Chapter 4b

CARCINOMA OF THE OESOPHAGUS

1. DEFINITION

This is one of the more frequent malignancies in humans. Attracting the ICD 10AM Code C25, it means a primary malignancy of the lining of the oesophagus which begins proximally at the pharyngo-oesophageal sphincter. As the oesophagus is lined with squamous epithelium, the usual malignancy is squamous carcinoma. However, with intrusion of the gastric glandular epithelium into the lower oesophagus, adenocarcinoma may affect the lower oesophagus and cardial region, a growing problem in western societies.

Among the clinical features of oesophageal carcinoma are:

- progressive dysphagia, generally painless,
- it is, in general incurable, with a relatively stable 5 year survival rate of about 5%
- it is rare under the age of 40,
- there is a marked racial variation in incidence.

Squamous carcinoma has an incidence of $2.6/10^5$ in the U.S. where is it four to five times more common in blacks than whites. Adenocarcinoma is rising in incidence in whites in recent years throughout most affluent societies; it has quadrupled in white males in the U.S. in recent decades whereas squamous carcinoma in blacks has doubled in the last 30 years, so that adenocarcinoma has overtaken squamous in incidence in the U.S. in whites. Males are affected more frequently than females overall in ratio of three or four to one.

2. EPIDEMIOLOGY

Squamous carcinoma and adenocarcinoma exhibit considerable differences in their epidemiological and other characteristics and will be considered separately.

2.1 Squamous Carcinoma

One of the remarkable features of this malignancy is the extraordinary variation in its incidence throughout the world leading to the view that there are major environmental and / or dietary factors in its causation. This is seen especially in China where 60% of the world's cancers occur. The incidence has been recorded as varying from 1.3 to $132/10^5$ in different Chinese counties and it seems that the incidence of carcinoma in humans mirrors the incidence of it in the gullet of chickens. (1) In Northern Asia there is a high carcinoma incidence belt extending through Kazakstan, Uzbekistan, Turkmenistan, Northern Afghanistan and the Caspian littoral of Iran. Whereas the incidence is high in the Transkei of South Africa and varying rates are seen in southern and eastern Africa, the disease is rare in the rest of Africa. These and similar factors lead inevitably to a dietary or environmental cause, at present unknown.

Suggested factors include:

- constituents of smoke from soft coal used for cooking – females who do not smoke are affected as often as males who do,
- nutritional deficiency, especially retinol, ascorbic acid, riboflavin, α tocopherol,
- a low fruit intake and ascorbic acid deficiency,
- selenium and molybdenum deficiency,
- nitrates and nitrites in high levels in plant tissue associated with a low soil molybdenum levels,
- contamination of water supplies by petroleum products.

2.1.1 Smoking and Alcohol

These are both associated with the development of squamous carcinoma and often coexist in the same patient; disentangling their relative importance is difficult. It is important to note that among well nourished, abstemious non-smoking males squamous carcinoma is virtually unknown. A group in Milan looked at 250 oesophageal cancer patients and 1089 controls. For 38 life-long non-smokers there was no difference between teetotallers and those having up to three drinks per day, with a statistically significant rise in OR to 3.6 for over eight drinks per day. On the other hand for 30 non-drinkers

there was a significant rise in trend with increasing smoking extending to an OR of 6.2 for smokers of more than 24 cigarettes per day (2). The same group attempted to estimate the Population Attributable Risk for these factors. In a study of 300 patients with oesophageal cancer and controls not only smoking and drinking but dietary β carotene were examined and found to be relevant (3) (Table 4.1). A study of 6701 Japanese/Americans in Hawaii showed a RR of 17.3 (6.7-44.2) in heavy smokers and drinkers compared with those who neither smoked nor drank heavily; in heavy drinking non-smokers, the RR was 8.6 (2.01-36.0) (4). In a population based cohort of 9353 individuals followed up for a mean of 7.7 years after treatment for alcoholism the S.I.R. of oesophageal cancer was 6.8 (4.5-9.9) although confounding by smoking was present (5).

2.1.2 Rare Causes

Rare but significant other causes include previous damage from corrosive ingestion for which the incubation period may be as long as 40 years for squamous carcinoma, and achalasia of the oesophagus. Patients with coeliac disease also have a small but significant elevation of risk. On the other hand there is good evidence for protective dietary factors, deficiency of which may contribute to the incidence of carcinoma associated with alcohol abuse.

Table 1. Population Attributable Risk (%) for oesophageal cancer

	Males	Females	Combined
Smoking	71	32	61
Alcohol	45	10	39
Low β carotene intake	40	29	38
Combined *	90	58	83

* assumption of a multiplicative model

One of the largest studies is an analysis of several data sets of case control studies in Northern Italy examining the dietary pattern of confirmed cases and controls. For the 294 oesophageal cancers, after allowance for various social factors including smoking, a multivariate RR of 0.2 for those in the upper tertile of fruit and vegetable consumption was found. Interestingly, there were positive benefits for all the epithelial cancers of the upper aero-digestive tract but no benefit for lymphomas and multiple myeloma (6). A multicentre French study of 208 cases of oesophageal

squamous cancer made similar findings. After adjustment for alcohol and tobacco use a beneficial effect of fresh fish, fruit and vegetables, vitamin A and vitamin D was found; the benefits of ascorbic acid were confined to heavy drinkers (7).

2.2 Adenocarcinoma

This is largely confined to the lower third of the oesophagus and is considered to arise from columnar epithelium extending up from the cardia (Barrett's oesophagus). Commoner in males it is increasing in incidence in western societies in parallel with adenocarcinoma of the cardia although distinction from carcinoma arising from the fundus of the stomach may be difficult. Many studies of risk factors do not distinguish it from squamous carcinoma and the significance of the major risk factors for squamous carcinoma, smoking and alcohol, in its production is not certain. It is however, associated with long standing reflux through Barrett's oesophagus. In Britain the adenocarcinoma rate for women is among the highest in the world. Multivariate analysis of 74 patients showed an OR for the highest quartile of weight around age 20 of 6.04 (1.28-28.52). For the highest quartile of fruit and vegetable consumption the OR was down to 0.08 (0.01-0.49). Breast feeding was also protective (OR=0.41) and duration dependent (P for trend 0.0005). The similar PAR for obesity in youth and low fruit intake was 90% to 96% with the breast feeding factor (8).

3. CLINICAL IMPLICATIONS

These are clear; whilst the adverse effect of alcohol has not been demonstrated for up to three drinks per day, beyond this it is clear that alcohol plays a significant role but it is probably exceeded by the effect of heavy smoking with relative risks of up to 6. However the effect of heavy alcohol use is significantly contributed to by the associated poor dietary intake of some of the micronutrients in fresh fruit and vegetables of which vitamin A, D and vitamin C are contributors. Traditionally, spirits have been regarded as being more dangerous than beverages of lower alcohol content but no firm data in support have been found.

The work of Negri's group (3) suggests that four of five cases of oesophageal squamous carcinoma may be attributed to the influence of smoking, heavy alcohol use and a nutritional deficiency in the form of β carotene deficiency. It is tempting to speculate how much other nutritional deficiencies contribute to the rest.

4. PREVENTATIVE STRATEGIES

That there is a nutritional aspect to oesophageal carcinoma has been clearly demonstrated in a nationwide Swedish controlled study of 608 cases (9). Fruit and vegetable consumption was inversely related to the risks of both types of oesophageal cancer but, surprisingly, not to adenocarcinoma of the cardia nearby, suggesting different factors for this type of tumour. Comparison of the highest quartile of intake (4.8 servings / day) with the lowest (1.5 servings) showed a lower risk of adenocarcinoma of 50% and a 40% reduction for squamous carcinoma. It was calculated that 20% of oesophageal squamous and adenocarcinomas were attributable to consuming fewer than three servings of fruit and vegetable per day. However, importantly from a public health point of view, over 25000 individuals would have to increase their fruit and vegetable consumption moderately to prevent one cancer per year. The findings corroborate the findings of the Italian study (3). We may safely conclude that the combination of heavy drinking, smoking and a low fruit and vegetable diet constitute a triad largely responsible for these carcinomas. As the authors point out, modifying the population intake achieves little. However, chemoprevention may have a role. A more recent metaanalysis of nine studies utilising data on aspirin, NSAIDs and both types of oesophageal cancer showed a protective effect of both aspirin and NSAIDs (OR=0.57, CI 0.47-0.71) overall (10). Aspirin was more protective (OR=0.5, CI 0.38-0.66). Dose response curves were noted. Before embarking on a chemoprevention program of aspirin in alcoholics, we need to recognise the life threatening haemorrhage that may follow its use in cirrhotic people.

References

1. Yang CS. Research on oesophageal carcinoma in China : a review. *Cancer Res.* **40**,2633-44 (1980).
2. La Vecchia C, Negri I. The role of alcohol in oesophageal cancer in non-smoker and of tobacco in non-drinker. *Int. J. Cancer* **43**,748-55 (1989).
3. Negri E, La Vecchia C, Franceschi S et al. Attributable risks for oesophageal cancer in Northern Italy. *Eur. J. Cancer* **28A**(6-7),1167-71 (1992).
4. Kato I, Nomura AM, Stemmermann EN, Chyou PH. Prospective study of the association of alcohol with cancers of the upper aerodigestive tract and other sites. *Cancer Causes Control* **3**,145-51 (1992).
5. Adami HO, McLaughlin JK, Hsing AW et al. Alcoholism and cancer risk : a population-based cohort study. *Cancer Causes Control* **3**,419-25 (1992).
6. Negri E, La Vecchia C, Franceschi S, D'Ananzo B, Parazzini F. Vegetable and fruit consumption and cancer risk. *Int. J. Cancer* **4**,350-4 (1991).
7. Launoy G, Milan C, Day NE et al. Diet and squamous-cell carcinoma of the oesophagus. *Int .J. Cancer* **76**,7-12 (1998).
8. Cheng KK, Sharp L, McKinney PA et al. Risk factors for oesophageal carcinoma in women in Britain. *Gastroenterology* **118** (Suppl 2), A 36 (2000).

9. Terry P, Lagergren J, Hansen H, Wolk A, Nyren O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancer. *Eur. J. Cancer Prev.* **10**,365-9 (2001).
10. Corley DA, Kerlakowske K, Verma R, Buffler P. Protective association of aspirin / NSAIDS and esophageal cancer : a systematic review and meta analysis. *Gastroenterology* **124**,47-58 (2003).

Chapter 5a

PEPTIC ULCER

1. DEFINITION AND OVERVIEW

Peptic ulcer is a benign, non-specific ulcer in those parts of the alimentary tract bathed in gastric juice. The ICD 10CM Codes are K26 for duodenal ulcer (DU) and K25 for gastric ulcer (GU). Histologically peptic ulcer is characterised by a loss of surface epithelium. In chronic ulcer, as discussed here, the defect extends through the muscularis mucosae and is associated with inflammatory changes and scarring on healing. These features distinguish it from acute ulcer / erosion which extends only into the lamina propria, does not penetrate the muscularis mucosae and readily heals as a rule without scarring. It appears to occur in most populations and there are isolated reports of ulcers dating back to Galen, who in the 2nd C A.D. treated Marcus Aurelius for what sounds like a peptic ulcer. Morgagni in 1737 described DU and GU and a case of perforated GU. However it appears that ulcer was a rare phenomenon with many isolated reports until the middle of the 19th C, at least in Europe (1). By the end of the 19th C, the disease was a cause of considerable morbidity and some mortality. From then there began an avalanche of studies on its physiology based upon acid and peptic digestion of the gastric mucosa, its diagnosis following the development of its roentgenographic detection in 1904, the development of gastric surgery following the first successful repair of a perforated ulcer in 1894 (2), and the promotion of elective gastric surgery by Berkeley Moynihan and his successors in Europe, the USA and the UK (3). Although this discussion is limited to gastric and duodenal ulcers, to be considered here, it is important to recognise that chronic peptic ulcer may occur rarely in other anatomical situations, in fact anywhere if acid and pepsin are both

present such as at or just beyond an anastomosis of stomach and small bowel, in a Meckel's diverticulum or in the oesophagus. These relative rarities are not discussed here.

2. DESCRIPTIVE EPIDEMIOLOGY

Gastric ulcer (GU) and duodenal ulcer (DU) share many features, not only in aetiology but in symptomatology; nonetheless there are important differences such as in pathophysiology. Although traditionally they are held to have real differences in symptoms, in the real world distinction based upon symptoms is hazardous. Moynihan, an early protagonist of surgery for DU at the turn of the 19th C emphasised the severe burning epigastric pain waking the patient at 2am, relieved by a glass of milk and occurring two, three or even four hours after meals with weeks of pain alternating with weeks or months of freedom in DU. "There are few diseases where symptoms appear in such ordered sequence as observed in duodenal ulcer" (3). This is in contrast to the traditional symptomatology of GU; pain soon after food, relieved by food or vomiting, which is not infrequent but again with periods of exacerbation and remission. In the modern western world such clear cut pictures are seldom seen and the distinction between ulcer and non ulcer dyspepsia at the bedside is not far removed from chance as the high prevalence of upper GI endoscopy in western society attests.

3. PREVALENCE

There are no good data on the prevalence of ulcer in any society: ulcer may be asymptomatic, there are practical and ethical difficulties in endoscoping large groups of patients for ulcer and PU may pursue a fluctuant course of activity and healing. In two endoscopic studies of 758 apparently normal asymptomatic volunteers, the prevalence of DU was 1.8% and of GU 1.1% (4). It is estimated that at least 10% of adult Americans have a lifetime chance of having a PU with a lower prevalence, possibly 4%, in women. A Danish study in the 1960's suggested that the annual incidence in men in Copenhagen was about $180/10^5$ for DU and $30/10^5$ for GU and in women the same study suggested that for DU the figure was half that for men and for GU the figures were approximately equal.

4. THE NATURAL HISTORY

"In general, although its interruptions to health are numerous, the menace to life of a duodenal ulcer is not great" (5). Contrary to a widely held belief, neither GU or DU poses a major threat to life expectancy. Most deaths are due to complications such as perforation or bleeding but when surgery was frequently employed, post operative death following elective surgery was the major cause of death. In spite of a vast literature on peptic ulcer, adequate data on the natural history of it are sparse. There are only eight studies using life table analysis, the only valid method and all have problems in validity (6). The studies suggest a small excess of deaths in the first year or two after diagnosis with death after elective surgery figuring prominently. The excess of deaths is more than compensated by a deficit of deaths from cerebrovascular disease. This may be due to the negative association between duodenal ulcer and hypertension to be discussed later.

5. COMPLICATIONS

An allied problem is that of the likelihood of complications and of subsequent death. As noted, the major cause of death was that following elective surgery with deaths from perforation or bleeding being fewer. The risk of bleeding or perforation is about 0.2 by 10 years with the risk of death from these heavily dependant upon age and concurrent disease. The risk of death from DU and GU is about equal because although DU outnumbers GU considerably it is much less likely to have a fatal outcome. The vulnerable group is that of elderly women with gastric ulcer (6).

6. ASSOCIATIONS

The list of alleged and proven associations, both positive and negative is long. Some, such as rheumatoid arthritis or chronic lung disease share a common aetiology such as NSAIDs or smoking. Others, such as a negative association with hypertension remain quite inexplicable. The list of definite associations is short, Multiple Endocrine Neoplasia (MEN) type I / gastrinoma / Zollinger-Ellison syndrome, systemic mastocytosis and basophil leukaemia, all rarities with a defined physiological base. Alleged associations include chronic bronchitis and emphysema, cirrhosis, chronic renal failure and chronic joint disease though the use of NSAIDs. The definition of association is rendered difficult by the near impossibility of determining who has an ulcer given the absence of symptoms in many

patients. There is another list (7) of claimed associations with no firm evidence. An association of GU and especially DU in younger men with coronary disease has been noted in an old study in the UK but smoking is likely to be the common factor (8). Strangely, there are also negative associations such as the strong negative association between DU and hypertension in males 40-49 (9). Another is between gastric cancer and DU (10) but there is, in spite of long held beliefs, no association of gastric cancer with GU (10).

7. SECULAR CHANGES

Over the last 150 years, dramatic changes in the prevalence of both DU and GU have taken place. However, an equally striking change has been the change in symptomatology. Although there are no literature references, personal experience of over 50 years strongly suggests that ulcers seen in earlier days often manifested more intense and prolonged symptoms than in recent years.

8. THE EFFECTS OF INTERVENTION

In spite of vast research and interventions into PU, there is a remarkable imbalance in the results achieved. Although elective surgery for ulcer was promoted from the turn of the 19^{th} C, scientific evaluation of the interventions was slow to eventuate. The earliest operations such as gastroenterostomy had the lowest mortality but unacceptably severe long term sequelae; over the decades it became evident that more radical operations carrying higher mortalities such as types of partial gastrectomy were more appropriate for long term outcomes and various operations to interrupt the gastric vagal supply also became more complicated. H_2 receptor antagonists led by cimetidine promised a new dawn but it was soon evident that although ulcer responded in what was then breathtaking speed, relapse rapidly took place on cessation. The next two discoveries brought greater promise. Proton pump inhibitors, capable of producing virtually complete paralysis of acid production and marketed in various molecular forms are superior to the H_2 receptor antagonists and are widely used but expensive. The discovery of *H.pylori* as a significant cause of ulcer offered the promise of eradication and an end to peptic ulcer but it too has problems. Its eradication regimen of co-administration of three drugs is not free of side effects and the ready tendency to drug resistance are unresolved problems.

9. GEOGRAPHY

Comparative data on the geographic aspects of PU are sparse. One cause is the fact that, until recently, diagnosis largely depended on radiology whose availability depends upon local socio-economic circumstances. Also in the middle of the 20th C when most of this work was done there were major social class determinants of ulcer. Everywhere DU outnumbers GU except in a fishing community in northern Norway and in Britain DU was more prevalent in Scotland than London. Striking differences in PU prevalence have been reported from Nigeria, Malaya and India (11). DU was said to be 15 times more prevalent in southern than in northern India. Moreover, in south India DU was much more frequent in the poor and rare in the upper classes. The PU in south India tended to stenose but not bleed or perforate. In western societies, DU was evenly distributed through the social classes but GU has tended to be largely restricted to the labouring classes (11). No comparable data from Europe or N. America appear to be available.

10. THE ULCER EPIDEMIC

Any mechanisms to explain the aetiology of peptic ulcer must accommodate what is not widely recognised; its epidemic character. In 1962, a detailed study using cohort analysis showed clearly that in males born in England and Wales in the middle of the 19th C the risk of ulcer appeared (12). This tendency to gastric ulcer reached its peak in those born about 1885 and for duodenal ulcer five years later. For females the graphs are more difficult to interpret. In all generations the risk of death rises with increasing age. After the peak in those born at the latter end of the 19th C the ulcer tendency fell so that now in the young in Western society the risk of death from peptic ulcer is vanishingly small. There have subsequently been similar results from studies in Germany, Switzerland, Japan, Western Europe and Australia (13). Susser and Stein speculated on the causes of the phenomenon and the possibility of a factor in the early urbanisation in Britain but the demonstration of similar changes in other different socio-political systems excludes this possibility. Hence, any hypothesis to explain the aetiology of peptic ulcer must explain the epidemic.

11. RISK FACTORS AND THE CAUSES OF PEPTIC ULCER

For close on a century intense research has focused on determining the cause of peptic ulcer but by the 1960s only two factors achieved any prominence – either some form of environmental influence such as diet and stress or heredity. However, with the growing use of epidemiological methods such as large scale controlled trials and cohort studies and better statistical techniques it has become apparent that there are a number of significant risk factors.

These are:

- *H.pylori*
- Non steroidal anti inflammatory agents (NSAIDs)
- Smoking
- Genetic factors

Other factors with less persuasive supportive evidence are:

- Diet – fibre, sugar, caffeine
- Stress
- Physical inactivity

We can now examine the various risk factors in the light of the epidemic.

11.1 H.pylori (Hp)

When rediscovered in 1982, *H.pylori* was hailed in some quarters as the cause of peptic ulcer. It is known to be present in the gastric mucus layer of about 95% of DU patients and in a smaller proportion of GU patients. Extensive studies show that being *H.pylori* positive increases the risk of PU 3.3 fold with the prevalence of the organism varying widely by age, geography and social class. In western societies the prevalence in the elderly is about 60% and in the young about 20%. Calculation of the PAR produces figures of about 0.3 in the young rising to about 0.58 in the elderly. Could Hp be a cause of the epidemic? A plausible explanation is that an epidemic of Hp began in the middle of the 19th C in also a large US study with an OR of 1.8 (15) and a study of 8006 Japanese Americans with an OR of 3.4 (2.4-4.7) for GU and 3.0 (1.9-4.7) for DU. A most impressive study is a long follow-up of British doctors showing a three fold increase in the risk of peptic ulcer in current smokers (16). However, it needs to be noted that a recent large cohort study showed no increase in risk of DU (17). Whatever the significance of ulcer production, it seems clear from two studies that there is a trebled risk of perforation in smokers (18, 19). In spite of this, smoking cannot be the cause of the PU epidemic. There are no Britain and spread around the world. Such pandemics are recognised such as

tuberculosis on a much attenuated time scale, diphtheria in Europe from 1858 and scarlet fever ten years later (13). However, Hp cannot be the complete explanation; even if the initial strain were of high pathogenicity with a OR of, say, five affecting 90% of the population the PAR only rises to 0.78.

11.2 NSAIDs

There is a large body of evidence to incriminate these as a cause especially for GU. An OR of about three is typical as is a background rate of about 0.08 for use of the drugs in western communities rising to about 0.5 in the elderly (13). Such figures give a PAR of about 0.12 overall and 0.5 in the elderly. However, while there is little doubt that NSAIDs are responsible for a considerable proportion of ulcers in the elderly, especially in elderly women and to a lesser extent in the young in contemporary western society, there is no case for it being responsible for the epidemic of ulcer because aspirin was not developed until 1899 and indomethacin, the first of the acceptable alternative NSAIDs, was not marketed until 1966.

11.3 Smoking

This is not uniformly accepted as causal in PU; among the difficulties in evaluation has been its association with alcohol use, for decades widely considered as having a role in PU. However recently there have been numerous clarifying studies. An OR of 2-3 is typical. There is a meta analysis of 20 studies (14) with an OR of 2.2 (2.0-2.3). There is data on the consumption of tobacco in the 19th C but it is clear that the rich smoked cigars and working men smoked pipes until refinements to cigarette making machines from 1881 led to a readily available and cheap form of tobacco. US consumption of cigarettes rose nine fold between 1875 and 1880 and World War 1 led to a major increase in tobacco consumption. The available data show a rise in trend in tobacco consumption in the US, UK, France and Germany to a peak around 1965 – 1980 and then a decline, especially in the UK. It is thus apparent that the rise of cigarette consumption coincided with the development of PU in the latter half of the 19th C. However, tobacco consumption continued to rise through the first half of the 20th C as the prevalence of ulcer fell. Perhaps the rise of the epidemic can be attributed to a pandemic of potent *H.pylori* with a rising use of tobacco products making a smaller contribution so that the waning *H.pylori* pandemic is the major contributor to the fall of PU prevalence in modern western societies. Of the other factors to be considered, the principal ones are:

11.4 Alcohol

While there is widespread belief in a role for alcohol in ulcer disease, the evidence is very slim. The outstanding study is a 13 year follow up study of British doctors which found no association (20). An NHAMES Study also found no association (17). There is another study reporting an increased OR of 2.4 (1.1-5.4) for the use of spirits, no effect with beer and a possible protective effect of wine (21).

11.5 Food and Diet

There is some evidence for dietary fibre having a role at least for DU. The NHAMES group found a strong negative association for soluble fibre and DU (17) RR 0.40 (0.22-0.74) and a similar negative association for Vitamin A RR 0.4 (0.23-0.91) for the highest quintiles of intake. There is also some evidence for a role for caffeine. A long follow up study of US college students found a 50% rise in the reported PU prevalence in those drinking carbonated drinks, almost certainly caffeine containing in that context, and a near doubling of incidence in those drinking more than 2 cups of coffee a day ($P<.01$) (22).

11.6 Heredity

Long a part of folklore, there is now clear evidence for an hereditary aspect of peptic ulcer. The principal evidence comes from two enormous twin studies. The Finnish Twin Cohort Study examined 13,888 same sex twin pairs followed for at least 30 years (23). There was a concordance of 23.6% in monozygotic and 14.8% in dizygotic twins for ulcer. Complex analysis showed that 39% of the liability to ulcer was explained by genetic and 61% by environmental factors. The Swedish Twin Registry Study (24) made similar findings with a genetic component in 66% of ulcer cases. The study also showed a strong genetic component in the liability to *H.pylori* colonisation with an hereditability of *H.pylori* at 0.63 which was independent of that for ulcer.

11.7 Stress

The evidence linking stress and PU is limited to a few reports and does not distinguish between DU and GU although DU has long been regarded as a badge of dedication in busy businessmen. A 9.2 year follow up of 5388 adults found a 1.9 ($P<0.05$) times increase in ulcer in those self reporting

stress with a positive dose response curve (15) and a Danish study showed a link between minor tranquilliser use and PU with an OR of 3 (21).

11.8 Physical Activity

There is only one study showing a major protective effect (OR=0.3) for moderate leisure time activity (21).

12. SUMMARY

It seems likely that the predominant causes of PU are the acquisition of Hp and smoking with a contribution from NSAIDs in the elderly. Genetic factors are important and govern the retention of Hp after its acquisition in childhood. Dietary and social factors have only a minor role if at all. Nevertheless, there remain many unsolved problems in the epidemiology of PU, but, in the western world, it is likely that the epidemic of ulcer will fade away before these problems are resolved.

References

1. Smith LA, Rivers AB. *Peptic ulcer: Pain patterns, diagnosis and medical management.* (Appleton Century Crofts, New York, 1953).
2. Perry EC, Shaw LE. On diseases of the duodenum. *Guy's Hospital Reports* **50**,171-308 (1894).
3. Moynihan BGA. *Duodenal Ulcer.* (WB Saunders, Philadelphia and London, 1910).
4. Adkamar K, Ertan A, Agrawal N, McMahon FG, Ryan J. Upper gastrointestinal endoscopy in normal asymptomatic volunteers. *Gastrointest. Endosc*. **32**,78-80 (1986).
5. Ryle JA. The natural history of duodenal ulcer. *Lancet* **1**,327-34 (1932).
6. Duggan JM. Is the aggressive management of peptic ulcer justified by the data*? J. Clin. Gastroenterol.* **17**,109-16 (1993).
7. Grossman ME (ed). *Peptic ulcer.: A guide for the practising physician.* (Year Book Medical Publishers, Chicago 1983)
8. Watkinson G. Relation of chronic peptic ulcer in coronary sclerosis. *Gastroenterology* **89**,292-301 (1958).
9. Medalie JH, Kahn KA, Neufeld HN, Riss E, Goldbourt E, Oron D. Association between blood-pressure and peptic-ulcer. *Lancet* **2**,1225-6 (1970).
10. Hansson L-E, Nyren O, Hsing AW, Bergstrom Q, Josefsson S, Chow W-H, Fraumeni JF, Adami HO. The risk of stomach cancer in patients with gastric or duodenal ulcer. *N. Engl. J. Med.* **335**,242-9 (1996).
11. Jones FA. Clinical and social problems of peptic ulcer. *Br. Med. J.* **1**,719-23 and 786-93 (1957).
12. Susser M, Stein Z. Civilization and peptic ulcer. *Lancet* **1**,115-9 (1962).
13. Duggan JM, Duggan A. What caused the epidemic of peptic ulcer? *In press*.
14. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer.: Nonsteroidal anti inflammatory drugs, Helicobactor pylori, and smoking. *J. Clin. Gastroenterol*. **24**, 2-17 (1997).

15. Anda RF, Williamson DF, Escobodo LG et al. Smoking and the risk of peptic ulcer disease among women in the United States. *Arch. Intern. Med.* **150**,1437-41 (1990).
16. Doll R, Peto R, Wheatley K et al. Mortality in relation to smoking : 40 years observations on male British doctors. *BMJ* **309** ,01-11 (1994).
17. Aldori WH, Giovannucci EL, Stampfer MJ et al. A prospective study of alcohol, smoking, caffeine and the risk of duodenal ulcer in men. *Epidemiology* **8**,470-4 (1997).
18. Svanes C, Soreide JA, Skarstein A et al. Smoking and ulcer perforation. *Gut* **41**,177-180 (1997).
19. Andersen IB, Jorgensen T, Bonnevie O, Gronbaek M, Sorensen TI. Smoking and alcohol intake as risk factors for bleeding and perforated peptic ulcers : a population based study. *Epidemiology* **11**,434-9 (2000).
20. Doll R, Peto R, Hall E. Mortality in relation to consumption of alcohol : 13 years observation on male British doctors. *BMJ* **309**,911-8 (1994).
21. Rosenstock S, Jorgen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease : a population based prospective cohort study comprising 2416 Danish adults. *Gut* **52**,186-93 (2003)
22. Paffenbarger RS, Wing AL, Hyde RT. Chronic disease in former college students XIII Early precursors of peptic ulcer. *Am. J. Epidemiol.* **100**,307-315 (1974).
23. Raiha I, Kemppainen H, Kaprio J et al. Lifestyle, stress, and genes in peptic ulcer disease : a nationwide twin cohort study. *Arch. Intern. Med.* **158**,698-740 (1998).
24. Malaty HM, Engstrand L, Pedersen NS et al. Helicobactor pylori infection : genetic and environmental influences : A study of twins. *Ann. Intern. Med.* **120**, 982-6 (1994).

Chapter 5b

CHRONIC GASTRITIS/GASTRIC EROSIONS

1. DEFINITION AND OVERVIEW

Chronic gastritis is a condition defined by a cellular infiltrate of chronic inflammatory cells in the gastric mucosa, attracting Codes ICD 10 AM K29.3, 29.4 and 29.5. A simple classification is:

- chronic atrophic gastritis Type A
- chronic atrophic gastritis Type B

And rare forms

- lymphocytic gastritis
- eosinophilic gastritis
- granulomatous gastritis
- Crohn's disease
- sarcoidosis

Chronic gastritis is a complex and confusing subject. Fortunately, the clinical and epidemiological aspects are fairly clear. The term is used in at least three aspects in medicine:

- clinical : a syndrome characterised by epigastric pain/discomfort, nausea, bleeding
- endoscopic : changes in the texture, colour, contour of the stomach at endoscopy
- histological : a variety of changes in mucosal cell nature and appearance, structure produced and nature of the cellular infiltrate.

Beyond this, it can be classified from multiple aspects:

- clinical
- endoscopic
- at least four histological classifications

- aetiological :
  - H.pylori
  - Immunological
  - Others
- topographic

To confuse the issue further:

- there is little or no correlation between the clinical, endoscopic and histological appearances
- changes in the mucosa are often patchy, so that the five standard biopsies from various parts often vary considerably in their appearance
- there are at least four current classifications, none used universally.

In chronic gastritis, the cellular infiltrate consists mainly of lymphocytes and plasma cells. The sequence is generally regarded as:

- Superficial gastritis. Inflammatory changes are limited to the lamina propria; the gastric glands are preserved with possibly a diminution of mucus in the glands.
- Atrophic gastritis. The inflammatory infiltrate extends deeper into the mucosa with progressive distortion and destruction of gastric glands.
- Gastric atrophy. The glandular structures are greatly diminished, as is the cellular infiltrate. The mucosa is thin and at endoscopy the changes are evident with vessels visible through the mucosa. This is one of the few occasions when a confident pathological diagnosis can be made at endoscopy.
- Intestinal metaplasia may be present in patches and predispose to gastric carcinoma.
- Type A gastritis is regarded as having an auto-immune basis and mainly effects the fundus and body of the stomach. It impairs gastric acid secretion and so is associated with hypo or achlorhydria, raised serum gastrin levels and, often, parietal and intrinsic factor antibodies. Its only significance is a small increase in the risk of gastric cancer. It occurs in two situations:

1. In pernicious anaemia. This is associated with parietal cell antibodies in 90% and with intrinsic factor antibodies in 40%.
2. Chronic gastritis (fundal) not associated with pernicious anaemia. In these patients about 60% have parietal cell antibodies but no intrinsic factor antibodies. Such patients may have relatives with pernicious anaemia.

- Type B chronic gastritis is associated with H.pylori colonisation (1). It begins and predominates in the antrum but may, over a period of 15 to 20 years extend to involve the whole stomach. In

its early stages H.pylori is readily demonstrated but as the atrophy progresses the organism it becomes more difficult to demonstrate (2). There is some evidence that treatment with H_2RA or PPI may hasten the onset of gastric atrophy and so theoretically of gastric carcinoma. There is also evidence that H.pylori organisms carrying the CagA genotype are the major culprit in the development of chronic gastritis type B.

2. RISK FACTORS FOR CHRONIC GASTRITIS

Although the acquisition of appropriate strains of H.pylori is regarded as the major determinant of type B gastritis, there are suggestions of other causes:

- alcohol abuse
- NSAIDs
- Duodenogastric reflux following gastric surgery

Apart from H.pylori infection, there are some infective causes, most of which are rare and seen mainly in the immunocompromised, as in AIDS

- viral - CMV and Herpes virus
- bacterial
- fungal

There are also granulomatous gastropathies

- Crohn's disease – quite uncommon
- Sarcoid – rare

References

1. Fontham ETII, Ruiz B, Perez A, Hunter F, Correa P. Determinants of Helicobactor pylori infection and chronic gastritis. *Am. J. Gastroenterol.* **90**,1094-1101 (1995).
2. Kuipers EJ, Appelmelk BJ. Helicobactor pylori and gastritis. *Biomed. Pharmacother.* **51**,105-5 (1997).

Chapter 5c

FUNCTIONAL DYSPEPSIA

1. DEFINITION

The word dyspepsia originates from the Greek (dys=bad and peptein= to digest) and the symptom was certainly familiar to the Greeks. In the first century A.D. Pliny recommended crushed coral for dyspepsia.

According to international consensus, (Rome II Working Party) functional dyspepsia is persistent or recurrent pain or discomfort centred in the upper abdomen without evidence of organic disease likely to explain the symptoms (1). It has also been styled nervous dyspepsia. The ICD 10AM Code is K31. It is characterised by bloating, nausea, early satiety, belching or upper abdominal fullness. There is overlap between functional dyspepsia and irritable bowel syndrome and so lower abdominal symptoms may also be present.

2. PREVALENCE

Functional dyspepsia affects between 20-54% of the adult population in western countries (2, 3). Most of these patients have no identifiable cause of dyspepsia by standard diagnostic tests and are classified as having functional dyspepsia (4). The overall prevalence of functional dyspepsia appears relatively stable but individually the disease is relapsing and remitting in nature (5).

3. NATURAL HISTORY

This is largely unknown. One study of such patients with a normal endoscopy found that symptoms spontaneously resolved in just over a third of patients. Follow-up studies show that organic disease is rarely diagnosed subsequently (6, 7). Cohort studies of symptom progression suggest that fewer than 10% of patients with functional dyspepsia are diagnosed with predominant reflux symptoms two years later and fewer than 5% with peptic ulcer disease (7). It is unclear whether this is higher than the rate of diagnosis of these diseases in the asymptomatic population. A study to evaluate this is needed.

4. MORBIDITY AND MORTALITY

Patients with functional dyspepsia have a normal life expectancy (8). However the condition does account for a large amount of morbidity in the community, much of it hidden. Only about 1 in 4 people with dyspeptic symptoms choose to consult a physician. Nevertheless because of the high prevalence of the disease and the chronic or recurrent nature of symptoms functional dyspepsia is a clinical problem of considerable cost to the health care system.

5. ASSOCIATIONS

Functional dyspepsia is associated with irritable bowel syndrome with a third of patent with functional dyspepsia also reporting IBS symptoms (9).

6. AGE AND GENDER

There is no evidence for a difference in the prevalence of functional dyspepsia between men and women. Few studies have analysed the prevalence of dyspepsia by age but some data report a fall in the prevalence of reported symptoms after the age of 50 years for both men and women (9, 10). Whether this correlates with a true fall in the prevalence of dyspepsia is unclear.

7. GEOGRAPHY

There is no convincing evidence that the epidemiology of functional dyspepsia is changing, but data on the prevalence in the lesser developed world are minimal**.**

8. EFFECTS OF INTERVENTIONS

A number of interventions have been tried for the treatment of functional dyspepsia. These include psychological intervention, acid suppression therapy, *H.pylori* eradication and prokinetic therapy. The reported benefits for all these therapies have been small if any. A systematic review of studies of psychological intervention has shown no overall benefit (11). Anti-secretory therapy may be effective but the effect seen in randomized trials may have been due to the inclusion of patients with organic disease. *H pylori* eradication therapy has a small but statistically significant effect in *H pylori* positive functional dyspepsia that may make it cost-effective treatment but the issue has been subject to considerable debate (12, 13). Prokinetic therapy has a small benefit if at all and is expensive and generally poorly tolerated.

9. AETIOLOGY

The pathophysiology of functional dyspepsia is only partially elucidated. However, there is growing evidence that functional dyspepsia is in fact a heterogeneous disorder. Several pathophysiologic mechanisms have been suggested. These include delayed gastric emptying (14), impaired gastric accommodation to a meal (15), hypersensitivity to gastric distension (16), *H. pylori* infection (17), altered response to duodenal lipids or acid (18), abnormal motility (19), or central nervous system dysfunction. In these respects, it shows a lot of characteristics with the irritable bowel syndrome.

Also, like irritable bowel syndrome, in some cases the onset of dyspepsia may be related to an infectious cause (20).

10. SUMMARY

Functional dyspepsia is a very common disorder in western society and a cause of considerable morbidity, much of it hidden. The cause is unknown and it may be a constellation of related disorders. Treatment, as a consequence, is most unsatisfactory, the evaluation being complicated by functional dyspepsia's tendency to spontaneous resolution.

References

1. Talley NJ, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GNJ. Functional gastroduodenal disorders. Gut 45,37-42 (1999).
2. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ III. Dyspepsia and dyspepsia subgroups: a population-based study. G*astroenterology* **102**,1259-1268 (1992).
3. Agreus L, Svardsudd K, Nyren O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. *Gastroenterology* **109**,671-680 (1995).
4. Penston JG, Pounder RE. A survey of dyspepsia in Great Britain. *Aliment. Pharmacol. Ther.* **10**,83-89 (1996).
5. Talley NJ; Weaver AL; Zinsmeister AR; Melton LJ 3rd. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am. J. Epidemiol.* **136**,165-77 (1992).
6. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* **343**,811-6 (1994).
7. Talley NJ, McNeil D, Hayden A, Colreavy C, Piper DW. Prognosis of chronic unexplained dyspepsia. *Gastroenterology* **92**,1060-6 (1987).
8. Lindell GH; Celebioglu F; Graffner HO. Non-ulcer dyspepsia in the long-term perspective. *Eur. J. Gastroenterol. Hepatol.* **7**,829-33 (1995).
9. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ. 3rd. Dyspepsia and dyspepsia subgroups: a population-based study. *Gastroenterology* **102**,1259-68 (1992).
10. Jones R, Lydeard S. Prevalence of symptoms of dyspepsia in the community. *BMJ* **298**,30-2 (1989).
11. Soo S, Moayyedi P, Deeks J, Delaney B, Lewis M, Forman D. Psychological interventions for non-ulcer dyspepsia. *The Cochrane Database of Systematic Reviews* 2004.
12. Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. *The Cochrane Database of Systematic Reviews* 2005.
13. Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. *The Cochrane Database of Systematic Reviews* 2003.
14. Waldron B, Cullen PT, Kumar R, et al. Evidence for hypomotility in non-ulcer dyspepsia: a prospective multifactorial study. *Gut* **32**,246-51 (1991).
15. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. *Gastroenterology* **115**,1346-52 (1998).
16. Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. *Gastroenterology* **121**,526-35 (2001).
17. Danesh J, Lawrence M, Murphy M, Roberts S, Collins R. Systematic review of the epidemiological evidence on Helicobacter pylori infection and nonulcer or uninvestigated dyspepsia. *Arch. Intern. Med.* **160**,1192-8 (2000).

18. Feinle C, Rades T, Otto B, Fried M. Fat digestion modulates gastrointestinal sensations induced by gastric distention and duodenal lipid in humans. *Gastroenterology* **120**,1100-7 (2001).
19. Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. *Gastroenterology* **91**,94-9 (1986).
20. Tack J, Demedts I, Dehondt G, et al. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* **122**,1738-47 (2002).

Chapter 5d

CARCINOMA OF THE STOMACH

1. OVERVIEW

Gastric cancer is the world's second most frequent cause of cancer mortality, surpassed only by lung cancer. The ICD 10AM Code is C16. It has been estimated that in 2000 it caused 870 000 deaths, equivalent to 12% of all cancer deaths. Occurring worldwide it is remarkably lethal with a pitifully low five year survival rate. A minority of 25-30% of patients present early enough for surgery and in societies such as the U.S. five year survival figures after surgery of 20% for distal and 10% for proximal lesions are typical. Gastric adenocarcinoma is radio resistant with the role of chemotherapy largely limited to palliation and limited remissions. A remarkable feature has been a major fall in incidence and mortality in western countries in the second half of the 20th Century, unrelated to medical intervention.

2. PATHOLOGY

About 90% of all gastric malignancies are adenocarcinoma. The remaining 10% consist of lymphomas and a smaller number of leiomyosarcomas with a minute contribution from rarities such as adenosquamous, squamous and undifferentiated carcinoma and malignant carcinoid. Adenocarcinoma will only be considered here; lymphoma is considered elsewhere.

The subdivisions of gastric adenocarcinoma are of some clinical significance. Histologically, it may be subdivided into a well differentiated

or intestinal type with cohesive cells forming gland like structures which often ulcerate, more frequent in older persons and males. The other, the diffuse type in which the cells are not adherent and infiltrate the gastric wall with thickening, sometimes called linitis plastica or leatherbottle stomach, occurs in younger persons and has a more even sex distribution. Gastric adenocarcinoma also tends to subdivide into an antral or body type which shows major variation in geographic distribution. The other type, cancer localised to the cardia shows a more uniform geographic distribution. It is the intestinal type of carcinoma which is mainly concerned in a major fall in incidence in recent decades in the west.

3. DESCRIPTIVE EPIDEMIOLOGY

The remarkable geographic variation is seen in comprehensive tables (1). The highest figure recorded is in Yamagata, Japan with an age adjusted incidence of $95.5/10^5$ in males; the lowest is in U.S. white males at $7.5/10^{5,}$ with a male to female ratio of 2:1 overall throughout the world. Data on the topographic localisation show the higher antral type age adjusted figures at $7.8/10^5$ in males in Hiroshima, Japan compared with the cardial figure of $4.6/10^5$. In U.S. whites non antral type cancer is 4.6 and cardial $2.9/10^5$. For antral type cancer overall the male to female ratio tends to be about 4:1 with a consistent 2:1 ratio for non cardiac cancer.

Ethnic groups migrating from high to low incidence areas have rates intermediate between their homeland and that of their new host with subsequent generations acquiring the rate of their new homeland. There are also major differences between ethnic groups in some countries. For example, in Singapore the age adjusted incidence varies from $29.3/10^5$ in ethnic male Chinese to $10.3/10^5$ in ethnic Indians and to $8.7/10^5$ in Malays.

Remarkable falls in both incidence and mortality rate in many countries in the latter half of the 20th Century have taken place. In Australia the age standardised rate has fallen from $25.9/10^5$ in 1950 to $6.7/10^5$ in 1994. By contrast in Japan the rate has more than halved but the fall was not apparent until the 1970's (1).

One of the mysteries of gastric cancer is the quite recent rise in the incidence of adenocarcinoma of the cardia and of the lower oesophagus, first observed in the latter part of the 20th Century. These changes began in the U.S. in the 1970's with a very high male to female ratio and a higher incidence in whites than in African Americans. There has been a five or six fold contemporaneous rise in cardial and lower oesophageal adenocarcinoma which is certainly real, even though it coincides with increased use of oesophago-gastric endoscopy (2). The changes, reported from the U.S., the

U.K., Switzerland and Australia are probably related to two factors. The first is gastro oesophageal reflux. A Swedish study has shown increasingly strong links between lower oesophageal and cardial adenocarcinoma and the increasing duration and intensity of reflux symptoms with an OR of 43.5 (18.3-103.5) for adenocarcinoma of the oesophagus and 4.4 (1.7-11) for carcinoma of the cardia but no link with oesophageal squamous causes (3). It has been proposed that obesity is the factor behind the reflux and the consequent reflux symptoms. The link may be through Barrett's oesophagus in which there is a sleeve of columnar gastric type of epithelium extending into the lower oesophagus, long regarded as having unquantified malignant potential (4). A more recent study shows a RR of 29.8 (9.6-106) for oesophageal adenocarcinoma in those with Barrett's, 4.5 (1.04-19.6) for oesophagitis and 3.1 (0.6-14.2) for those with reflux symptoms (5). Unfortunately there are as yet no comparative data for cardial cancers.

The other factor thought to be relevant is dietary. There is a strong inverse relationship between cardial cancer and dietary fibre intake (P trend < 0.0001) (6).

4. AGE, SEX AND RACIAL FACTORS

The incidence rises with age; most patients are 50 to 70 years of age and the sex ratio has been noted. The racial differences are quite marked, for example, in Singapore as noted above.

5. SOCIOECONOMIC FACTORS

In general, there is a marked social gradient with higher rates in the lower socioeconomic classes but the opposite is true in the newly observed cardial cancers which mainly effect the professional classes.

6. RISK FACTORS AND AETIOLOGY

6.1 H.pylori

This was classified by the International Agency for Research on Cancer as a carcinogen in 1994. The data are compelling and the best explanation for the geographic variation, falling incidence and socioeconomic gradient observed. This link however does not extend to carcinoma of the cardia.

Metaanalysis of prospective cohort studies of those infected with *H.pylori* show increasing risk with time rising to almost 9 in the 15 year follow up group (7). The mechanism proposed is the inevitable chronic gastritis engendered by *H.pylori* infection. The CagA virulence factor of *H.pylori* is associated and its absence carries, at most, a low risk. It has been proposed that absence of *H.pyori* indicates a minimal risk of gastric cancer.

6.2 Gastric Surgery

Debatable for decades, there has recently been a spate of papers (8). The evidence is that there is a small increase in the risk of gastric cancer on prolonged follow up of patients after partial gastrectomy.

6.3 Peptic Ulcer

As gastric and duodenal ulcer and carcinoma all share *H.pylori* as a risk factor, peptic ulcer disease might be expected to be a risk factor for cancer but the reality is different. Duodenal ulcer brings a diminished risk of cancer but gastric ulcer betokens a small increase in risk other than at the cardia. A novel explanation has been proposed (9).

6.4 Dietary Factors

The wide variation in prevalence of gastric cancer between nations, ethnic groups, socioeconomic classes, over time and in migrant groups strongly suggests a role for dietary factors in the development of gastric carcinoma. The strength of various factors varies (1).

6.4.1 Fruit and Vegetables

There is powerful evidence of a constituent of fruit and vegetables being protective. The principal factors suggested have been vitamin C and E, carotenoids (especially β carotene) and selenium. Although a high intake of dietary vitamin C has been linked with a halving of carcinoma rates, a very large intervention study in China was not supportive. A most intriguing study has explored the long held belief that allium vegetables (onions, leek, garlic) were protective. A large cohort study of diet and risk found that for the 139 gastric cancer and 3123 controls the risk of body but not cardial cancer was reduced to 0.5 (0.26-0.95) in those eating at least 0.5 onions daily but that other allium vegetables were ineffective (10).

6.4.2 Salt

Although a high dietary salt intake has been linked in many studies with increased risk, the evidence remains inconclusive.

6.4.3 Nitrite and Nitrate

N – Nitroso compounds, particularly nitrite and to a lesser extent nitrate, have been incriminated but the evidence is confusing. Nitrate is found especially in vegetables which also have a protective effect. Nitrites mainly come from preserved meat which characteristically also has a high salt content. Ultimately, these complexities merely suggest a small increase in risk with high nitrites which are abolished by a high fruit and vegetable intake.

Ultimately, with the complexity of food composition and changes in food preservation and cooking and growth of refrigerators, the role of specific nutrients in the prevention or causation of gastric cancer and the contemporary fall in its incidence must remain largely speculative.

6.5 Ionising Radiation

Studies of the Japanese atomic bomb survivors and of those exposed to therapeutic radiation to the epigastrium show small increases. The atomic survivors show a highly significant linear increase in risk with radiation dosage but the attributable risk, given the high rate of gastric cancer in the Japanese, was only 6.5%. For occupational exposure in the radiography industry no increase has been found.

6.6 Pernicious Anaemia

Long recognised, the conclusive study shows a three fold increase in risk at 20 years.

6.7 Smoking

Another complex situation, this remains unclear. Smoking studies are confounded by the association with *H.pylori* which may well relate to it and an increasing likelihood of a diminished fruit and vegetable intake with increased smoking.

6.8 Alcohol

Overall, the vast evidence base does not support a linkage.

6.9 Asbestos Exposure

Overall, the evidence does not support a linkage.

7. HEREDITARY FACTORS

Long recognised has been the familial tendency to gastric cancer but the massive Scandinavian Twin Studies have clarified the issue. Model fitting to the complex data shows that hereditary factors contributed 28% (0-51%), shared environmental factors 10% (0-34%) and environmental factors 62% (0-76%) to the development of gastric carcinoma. The high genetic contribution should occasion little surprise given recent evidence for a major genetic contribution to *H.pylori* acquisition (11).

In summary, while cancer of the gastric body rapidly diminishes in western society, we are witnessing the onset of a new manifestation; adenocarcinoma of the cardia and lower oesophagus, particularly in males linked to reflux and obesity. Simultaneously *H.pylori* is taking a diminishing role. If its prevalence is now only about 50% in older persons and it increases the risk by a factor of about 2.5 (12), then the PAR is only about 40%.

Ironically as western society becomes more affluent and hygienic, losing its *H.pylori* and gaining weight, it loses its propensity to carcinoma of the body of the stomach but acquires a higher risk of cardial cancer.

References

1. Kelley JR, Duggan JM. Gastric cancer epidemiology and risk factors. *J. Clin. Epidemiol.* 56,1-9 (2003).
2. Blot W, Devesa SS, Klneller R W et al. Rising incidence of adenocarcinoma of the oesophagus and gastric cardia. *JAMA* 265,1287-9 (1991).
3. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux is a risk factor for esophageal adenocarcinoma. *N. Engl. J. Med.* 340,825-31 (1999).
4. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cadia. *Ann .Intern. Med.* 130,883-890 (1999).
5. Solaymani – Dodaran M, Logan RFA, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Gut* 53,1070-4 (2004).
6. Terry P, Lagergren J, Ye W, Wolk F, Nyren O. Inverse association between intake of cereal fibre and risk of gastric cardia cancer. *Gastroenterology* 120,387-391 (2001).
7. Forman D, Webb P, Parsonnet J. Helicobactor pylori and gastric cancer. *Lancet* 343,243-4 (1994).

8. Duggan JM, Zinmeister AR, Kelly KA, Melton LJ III. Long-term survival among patients operated upon for peptic ulcer disease. *J. Gastroenterol. Hepatol.* 14,1074-82 (1999).
9. Parsonnet J, Friedman GD, Orentreich N, Vogelman N. Risk of gastric cancer in people with Cag A positive and Cag A negative Helicobactor pylori infection. *Gut* 40(3),297-301 (1997).
10. Dorrant E, Van Den Brandt PA, Goldbaum RA, Sturmans F. Consumption of onions and reduced risk of stomach carcinoma. *Gastroenterology* 110,12-20 (1996).
11. Malaty HM, Graham BY, Isaksson I, Engstrand L, Pedersen NI. Are genetic influences on peptic ulcer dependent or independent of genetic factors for Helicobactor pylori infection. *Arch. Intern. Med*. 160,105-9 (2000).
12. Danesh J. Helicobactor pylori and gastric cancer : systematic review of epidemiological studies. *Aliment. Pharmacol. Ther.* 13,851-6 (1999).

Chapter 6a

COELIAC DISEASE/CELIAC SPRUE

1. DEFINITION

Coeliac Disease, Celiac Sprue in North America, is a disease characterised by changes in the mucosa of the upper small intestine. These changes, which begin in the duodenum, are of extremely variable extent and degree. They are characterised by a lymphocytic infiltrate of the mucosa and evidence of damage leading to blunting and even loss of villi and co-incident hypertrophy of their precursor cells in the mucosa. These changes may lead to defective absorption of nutrients, especially folate and iron whose absorption is localised to the duodenum. The ICD 10CM Code is K90.0. In severe cases there are widespread absorptive defects, manifested as diarrhoea with steatorrhoea, malnutrition and ill health. In this case it generally manifests in infancy but increasingly it is being recognised as producing subtle changes in health which may not manifest until late adult life.

2. PATHOLOGY

The central feature of coeliac disease is this change in architecture of the upper small intestine with damage to, or loss of villous processes, due to an extraordinary complex series of changes within the mucosa.

The molecular basis of coeliac disease resides in a genetic abnormality wherein peptide residues of gliadin molecules gain entrance to the lamina propria where macrophages dendritic or B cells containing the HLA class II DQ2 or DQ8 haplotype attach to them. These present them to T cells

containing the α/β receptor which in turn activate other lymphocytes to liberate cytokines, in particular interferon γ, interleukin 4 and Tumour Necrosis Factor α. These damage the submucosa liberating transglutaminases, serum markers for the disease which are liberated from the lamina propria. The role of the transglutaminases is to deaminate the glutamine residues, the transglutaminase levels rise and provoke T cells to produce the transglutaminase antibodies so characteristic of the disease. In Western Europe the prevalence of HLA DQ2 and DQ8 is 25-35%; why only one in 20-30 bearers of this develop coeliac syndrome is a mystery (1).

3. EPIDEMIOLOGY

It is being recognised as a fairly common disorder in white societies with a prevalence estimated at 1 in 120-300 in Europe and North America. In the US, a large multicentre study revealed a prevalence of biopsy proven disease of 1:133 in the population and 1:22 in first degree relatives (2). In other studies it was 1:13 in first degree relatives. It is seen most often in Western Europe and North America and in European migrants to North America and Australasia with the highest prevalence reported to be in those of Celtic origin. Though studies are sparse it is being increasingly reported in the Middle East. In contrast, it is rare in blacks, Chinese and Japanese and uncommon in Indians and has a slight female predominance. The ultimate cause is regarded as immunologic. Patients with coeliac disease have a genetic defect with an inability to handle prolamines which are nitrogen rich proteins.

The background to the development of gluten sensitivity is of some interest. Some 10,000 years ago in Mesopotamia some of the grasses underwent a series of strange genetic transformations out of which emerged a new grass with six sets of chromosomes. This grass, a prolific producer of large seeds with a high protein content was thus of high nutritive value both in quantity and in quality - wheat. As use of wheat and barley slowly spread through the fertile crescent from the Valleys of the Tigris and Euphrates across Turkey to the Levant and later beyond to Western Europe as a storable food source of considerable nutritive value it provided a basis for the development of Middle Eastern and Western civilization.

4. CLINICAL MANIFESTATIONS

The disease has been likened to an iceberg in that, of those with the disease, a few have gross symptoms and signs evident, many have mild

symptoms or signs and many are apparently symptom-free. Its manifestations are extraordinarily variable; gross cases have diarrhoea, wasting, pot belly and marked impairment of well being. At the other end of the scale are numerous patients asymptomatic or only mildly symptomatic with protean manifestations such as lethargy, mild anaemia, infertility or osteoporosis (3). It is also apparent that screen detected Coeliac patients do not differ from controls on their SF36 indices which are unaffected by a gluten free diet(4). The picture is rendered more complex by the finding that there are people with the molecular abnormality of coeliac disease with no detectable trace of the disease. An hypothesized explanation is that those with the disease have been sensitized by a particular strain of adenovirus which has, in its constitution, an amino acid sequence identical to a crucial one found in gliadin. Prolamine content is highest in wheat, then barley, then rye, then oats but there are no prolamines in maize or rice. It appears that the small amounts in oats are insufficient to present any problems to coeliac patients (5). The disease runs strongly in families. First degree relatives of those with coeliac disease have a 22% risk of the disease but in identical twins the concordance rate is only 70% so that there is a powerful argument against the genetic defect being the whole story in the pathogenesis of the disease.

5. RISK FACTORS FOR COELIAC DISEASE

There are two necessary but insufficient causes for coeliac disease. Firstly there must be a particular cell surface antigen on lymphocytes whose presence is determined by a gene on chromosome 6 ie: the HLA Class II DQ2 or DQ8 must be present. Secondly, there must be exposure to a specific amino acid sequence which is found in the alcohol soluble fraction of gluten, gliadin in wheat, hordein in barley or secalin in rye. A strange but unexplained risk factor for coeliac disease is cigarette smoking. Suspected for some time, a recent study has proved the link (6). A comparison of 138 cases and 276 age and sex matched controls showed that 10% of cases but 30% of controls were current smokers, OR=0.21 (95%C.I. 0.11-0.40). For current heavy smokers the OR=0.15 (95% C.I. 0.06-0.37). As in ulcerative colitis where a similar protective effect of smoking has been shown the question of what advice to give to a smoker with or at risk of the disease arises. The literature so far appears devoid of any in-depth analysis but one is warranted. A large twin study has clarified some of these issues (7). For dizygotic twins (DZ) there was no increase in the risk of CD in the other twin, whereas for monozygotic twins (MZ) the OR was 17 (2.1-134.0) The data suggest firstly that environmental factors played a role and secondly

that there may be other genes involved. However not all the subjects submitted to biopsy and with time the concordance rates for coeliac disease in twins may increase.

6. ASSOCIATED DISORDERS

There are three types of associated disorders:

1. Those probably part of the coeliac syndrome.
2. Conditions sometimes associated with the coeliac syndrome.
3. Complications.

1. Conditions probably part of the coeliac syndrome.
   - IgA deficiency. This immunological abnormality is associated with increase of coeliac disease. A side-effect of this is that limiting testing for the antibodies characteristic of coeliac to the IgA class is a cause of false negative results.
   - Down syndrome. In this the prevalence of coeliac disease increased 20-40 times over controls (8).
   - Dermatitis Herpetiformis - In these patients coeliac disease is present in at least 70% but strangely, the manifestations are mild. They may even be absent but be brought to light by a prolonged high gluten diet. Adoption of a gluten free diet is said to control the disease.
   - Diabetes Mellitus - There is a definite but unexplained link between the presence of IDDM (insulin dependent diabetes mellitus) and that of coeliac disease which operates in both ways. Studies of IDDM show a prevalence of coeliac disease in IDDM patients of 2.6%, 4.9%, 2.6%, 1.8% and 4.6% (9). Contrariwise in a study of coeliac disease (10) the prevalence of IDDM in coeliac patients of 5.4% was higher than that in control patients (1.5%) The typical sequence is IDDM followed by the onset or diagnosis of a mild form of coeliac disease.
   - Infertility - In both males and females, infertility is said to occur in coeliac disease. However, a recent very large community study shows that women with coeliac disease have the same number of live births as controls but have them later and have more caesarean sections consistent with a socioeconomic or educational advantage of women with coeliac disease (11).

2. Conditions in which the coeliac syndrome has increased prevalence (3). This list is constantly being added to and the links vary in strength from proven and significant such as liver disease and IDDM to curiosities such as alopecia areata. Of this extraordinary list of conditions the more important

ones at present appear to be the diabetes, chronic liver disease, and there is growing evidence for a high prevalence of coeliac disease in the irritable bowel syndrome (12). The changes are by and large unexplained and are not thought to be strictly complications. The babies of a mother or father with coeliac disease are more likely to be in the low birth weight category (13).

Most complications of coeliac disease relate to the metabolic effects of disease such as anaemia from malabsorption of iron, folate or Vitamin B_{12} or osteomalacia related to calcium and/or Vitamin D malabsorption.

The principal life threatening complications are:

- Lymphoma
- Carcinoma of the oral cavity and oesophagus
- Ulcerative jejunitis
- Collagenous sprue

By far, the most important, frequent and feared is lymphoma which is greatly increased (RR77.8,$p<0.001$) in a study of 210 patients not on a gluten free diet with a long follow up. For cancers of the mouth and pharynx (RR=9.7) (oesophagus 12.3) the risk was significantly increased. However it needs to be emphasised that in patients adhering to a gluten free diet, these risks appear to be totally abolished (14).

7. DIAGNOSIS

Until the 1990's the diagnosis was largely made on the appearances of a biopsy specimen taken in the upper small intestine, originally by various capsule arrangements but more recently by biopsies taken through an endoscope. However during the 1990's major developments have taken place in the detection and interpretation of serological changes. These have greatly facilitated the detection and the management of the disease. The first of these to attain any credence was the gliadin antibody but this has been largely superseded. An endomysial antibody contained within the IgA component of serum directed against smooth muscle bundles has proved to be a very good test for coeliac disease. Its sensitivity is close to 100% as is its specificity. More recently another IgA constituent, an antibody to the enzyme transglutaminase has been shown to be of outstanding value in the diagnosis of coeliac disease with almost 100% sensitivity and specificity. The histological changes in the small bowel biopsy may not be gross and indeed it is now evident that there may only be subtle changes with an increase in lymphocytes within the lamina propria in such cases . It is also becoming apparent that a high gluten diet administered over some weeks or months may make these changes more apparent. The changes in the small

bowel mucosa may also be patchy so that a normal biopsy does not totally exclude the diagnosis.

8. PROGNOSIS

Until recent decades it was widely held that the disease was associated with an undue incidence of epithelial tumours particularly of oesophagus and gut lymphoma. However it is now clear that with a gluten free diet the expectation of life in patients with coeliac disease is normal.

References

1. Schuppan D, Esslinger B et al. Innate immunity and coeliac disease. *Lancet* **362**,3-4 (2003).
2. Fasano A, Berti I, Gerarduzzi T et al. Prevalence of coeliac disease in at-risk and not-at-risk groups in the United States. *Arch. Intern. Med.* **163**,286-292 (2003).
3. Duggan JM. Coeliac disease : the great imitator. *Med. J. Aust.* **180,**524-6 (2004).
4. Johnston SD, Rodgers C, Watson RGP. Quality of life in screen detected and typical coeliac disease and the effect of excluding dietary gluten. *Eur. J. Gastroentero.l Hepatol.* **16**,1281-6 (2004).
5. Janatuinen EK, Kemppainen TA, Julkunen RJK et al. No harm from five year ingestion of oats in coeliac disease. *Gut* **50**,332-5 (2002).
6. Suman S, Williams EJ et al. Is the risk of adult coeliac disease causally related to cigarette exposure? *Eur. J. Gastroenterol. Hepatol.* **15**,995-1000 (2003).
7. Greco L, Romino R, et al. The first large population based twin study of coeliac disease. *Gut* **50**,624-8 (2002).
8. Duggan JM. Down's syndrome is strongly associated with coeliac disease. *Gut* **40**,492-6 (1997).
9. Sjorberg K, Eriksson KF et al. Screening for coeliac disease in adult insulin-dependant diabetes mellitus. *J. Intern. Med.* **243**,133-140 (1998).
10. Collin P, Reunala T et al. Coeliac disease - associated disorders and survival. *Gut* **35**,1215-8 (1994).
11. Tata LJ, Card TR, Logan TFA, Hubbard RB, Smith CJP, West J. Fertility and preganacy – related events in women with coeliac disease : a population based cohort study. *Gastroenterology* (in press).
12. Duggan JM. Coeliac disease the great imitator. *Med. J.Aust.* **180**,524-6 (2004).
13. Ludvigsson JF, Ludvigsson J. Coeliac disease in the father affects the newborn. *Gut* **49**,169-175 (2001).
14. Holmes GKT, Prior M, et al. Malignancy in coeliac disease - effects of a gluten free diet. *Gut* **30**,333-8 (1989).

Chapter 6b

LACTASE DEFICIENCY

1. OVERVIEW

Lactase deficiency is widespread throughout the world and is not really a disease: it is normal for young mammals designed to derive energy from maternal milk containing lactose to progressively lose their lactase after weaning. Adult mammals do not normally have access to milk so the possession of small intestinal lactase is redundant. In humans lactase activity falls at about age five. In nature, lactose only occurs in milk; in virtually all placental mammals except sea lions, lactose is the carbohydrate in milk: in macropods such as kangaroos milk does not contain lactose so that baby kangaroos (Joeys) reared on cow's milk develop cataracts from galactosaemia from their inability to metabolise galactose. However in Northern Europeans and in those living in the north-west of the Indian Subcontinent, lactase tends to persist in the adult, probably because there is a survival advantage in being able to utilise milk products such as cheese, through the winter when food supplies may be limited. Interestingly, the Dutch, renowned for their dairy products such as cheese, have the lowest prevalence of lactase deficiency of any group studied. We may conclude that lactase deficiency (so called alactasia or lactose intolerance) is not a disease but that the persistence into adulthood of lactase is a biological adaptation to the use of milk products in certain societies. The ICD 10AM Code is E73.

Lactase is an enzyme found in the brush border of the small intestine. It breaks down lactose into the six carbon sugars glucose and galactose. From the duodeno-jejunal junction its concentration rises rapidly to a plateau at about 50cms from the duodenal-jejunal junction and declines rapidly from

about 150cms to 0 at the ileocaecal junction but the histology of the small intestine is quite normal.

The frequency of lactase deficiency varies throughout the world.

Table 2 . Prevalence of lactose intolerance (1)

Group	**Prevalence %**
Orientals in the US	100
Black Americans	81
Italians	71
Australian aborigines	67
White Americans	24
Dutch	0

There is a major discordance between the intestinal levels of lactase and the symptomatology. The typical picture is of discomfort soon after milk or milk products. This may take the form of colicky abdominal pain, nausea, a sense of abdominal distension with flatus and possibly brief, brisk, watery diarrhoea. Many people have no symptoms at all with the level of symptoms being modified by factors such as dose of lactose, accompanying food and fibre, the rate of intestinal transit and the colonic flora. Lactose escaping to the colon may be rapidly metabolised by the resident flora without production of symptoms. The range of tolerance to lactose in those deficient in it is illustrated by the fact that one study showed that 50g of lactose will produce symptoms in 70-80% of lactose malabsorbers whereas 10g, such as contained in 200 mls in a glass of milk will only produce symptoms in 30-60% of subjects. (2)

2. DIAGNOSIS

This may be suggested by a dietary history and the effect of milk upon symptoms, the symptomatology overall and the ethnic background of the patient. Various diagnostic approaches have been suggested. A brisk response to a milkshake is virtually diagnostic but lacks sensitivy. At the other end of the scale is small bowel biopsy with analysis of the enzyme level in a biopsy specimen. Lactose tolerance tests are less invasive. One

involves the measurement of blood glucose levels or breath hydrogen levels after a lactose load.

3. SECONDARY LACTASE INTOLERANCE

This occurs in a number of situations. A standard one is post gastrectomy due to the rapid dumping of gastric contents into the intestine. It also occurs in small bowel mucosal diseases such as coeliac disease, tropical sprue, or short bowel syndrome. It has been also reported in other mucosal disorders even duodenal ulcer.

4. MANAGEMENT

The vast majority of patients will respond to a low lactose diet with the restriction of obvious milk products, it is said that rarely patients are even sensitive to the minute amount of lactose in some tablet formulations. The form of the food is important. It has been claimed that equivalent amounts of lactose given as yogurt are much better tolerated than lactose alone (3). Particularly in children, it is essential to provide an alternative source of calcium. Scrutinizing of food labels is also important. Commercially, "lactase" preparations, really bacterial or yeast β galactosidases are available and of variable value. Live culture yoghurt, which contains endogenous β galactosidase is an alternative containing both calcium and calories. Essentially the management of lactose intolerance consists of tailoring the lactose component of the diet to the patient's tolerance; little is gained by the use of a lactose free diet if the patient can tolerate some lactose.

5. PROGNOSIS

Lactose intolerance has no complications and once established apparently by the primary form is permanent.

6. SECONDARY FORMS

The prognosis of secondary forms depends upon adequate restoration of normal small intestinal anatomy. There is a very rare congenital form of alactasia, a condition with severe consequences for a neonate.

References

1. Buller HA, Grand RJ. Lactose intolerance. *Annu. Rev. Med.* **41**,141-8 (1990).
2. Gudmand-Hoyer E, Simony V. Individual sensitivity to lactose malabsorption. *Am. J. Dig. Dis.* **22**,177-81 (1977).
3. Kolars J, Levitt MD, Anouiji M, Savaiano DA. Yogurt - auto digestive source of lactose. *N. Engl. J. Med.* **310**,1-3 (1984).

Chapter 7a

IRRITABLE BOWEL SYNDROME

1. DEFINITION

Irritable bowel syndrome (IBS) is a functional bowel disorder for which no structural or biochemical explanations have been found. It has also been called mucous colitis, spastic colon and irritable colon. The ICD 10AM Code is K58.

2. DIAGNOSIS

Diagnosis can be made by using either the Manning (validated) or Rome II criteria (recommended but not validated). The term is often misused, partly because, in practice, its definition defies ready precision.

2.1 Manning Criteria for IBS (1)

1. Pain eased after bowel movement
2. More frequent bowel movements at onset of pain
3. Looser stools at onset of pain
4. Visible (abdominal) distention
5. Feeling of incomplete evacuation
6. Passage of mucus

2.2 Rome II criteria for IBS (2)

- At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features;
- Relieved with defecation; and/or
- Onset associated with a change in frequency of stool; and/or
- Onset associated with a change in form (appearance) of stool
- Symptoms cumulatively supporting IBS diagnosis
- Abnormal stool frequency
- Abnormal stool form (lumpy/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

In all cases, the diagnosis is contingent upon the exclusion of other and organic conditions; it is essential that bleeding, overt and occult and other possibly sinister findings be excluded. Symptom subtypes - constipation predominant, diarrhoea predominant and alternating type symptomatology have limited value as patient and doctor view may differ (3). IBS is associated with substantial morbidity but no mortality. Compared with the population, IBS sufferers report a poorer general state of health and higher absenteeism (4). In the U.S. IBS is the most common cause for referral to a gastroenterologist and accounts for 3.5 million physician visits, 2.2 million prescriptions and 35,000 hospitalizations p.a. with similar figures reported for Europe and the U.K. (5).

3. PREVALENCE

Most community based studies report a population prevalence of 10-20% in developed countries using the different definitions. It has been reported in less developed countries but the data are sparse (4, 6, 7).

4. NATURAL HISTORY

IBS is a chronic disorder with fluctuating symptoms. Longitudinal studies show a turnover of those affected, with similar proportion reporting loss of symptoms and new symptomatology (8). It is not associated with any known complications or shortening of life expectancy.

5. ASSOCIATIONS AND POSSIBLE CAUSAL FACTORS

More than 80% of patients with IBS have dyspepsia; in the majority of these the dyspepsia is functional. Psychological vulnerability and the experience of having problems have been strongly associated with the prevalence and incidence of IBS (9). Psychological morbidity has been associated in many studies with consulting behavior in general and IBS in particular (7, 10).

6. AGE

Prevalence may decline with age but this may be due to reporting bias (4). In a population-based cohort of 2956 newly diagnosed irritable bowel syndrome patients aged 20-79 years, Ruigomez found only 12% were 60 years or older (11) .

7. GENDER

IBS predominantly affects women (4, 11). Clinic based studies have a female to male ratio of 3-4 to 1, higher than the ratios of 2:1 seen in community studies.

8. GENETIC FACTORS

There is limited evidence for a genetic role in IBS (12). Twin studies show IBS is twice as frequent in monozygotic compared with dizygotic twins (13). Environmental factors more than genes may be important in pathogenesis although genes may determine susceptibility to post infective IBS (13).

9. EFFECTS OF INTERVENTION

Surprisingly few drugs have demonstrated effectiveness in IBS. The antidiarrhoeal loperamide and opoids have been shown to be effective in those with diarrhoea. Tricyclic antidepressants have been shown to be effective in one meta-analysis (NNT=3) (14). Serotonin receptor agonists

and antagonists are currently being trialed however their effectiveness may be outweighed by their side-effect profile.

10. CAUSES

The main contenders for causing IBS are visceral hypersensitivity, motor abnormalities, psychosocial distress and infection and inflammation.

Post infective IBS accounts for 6-17% of IBS (15). Up to 33% of bacterial gastroenteritis will result in IBS, however, there are few case control studies to indicate relative risk (16). Reported risk factors for post infective IBS include psychological vulnerability (RR=2, 95% CI1.7-2.4), female gender (RR=3.4, 95%CI 1.1-9.8), duration of infective illness (RR=11.4, 95%CI 2.2-5.8) and bacterial toxin (RR=10.5, 95%CI 1.4-7.6) (17, 18). A case review of over 500,000 general practice records found the incidence of new cases of IBS amongst those with a reported history of gastroenteritis to be 0.3% and 4% giving an adjusted relative risk of 11.9% (95% confidence interval 6.7 to 21.0).

The role of visceral hypersensitivity and motor dysfunction is controversial.

Only a minority of patients with IBS seek medical attention. Even so, IBS patients represent up to half of those presenting in gastroenterological practice. Whilst those who do not seek help do not differ from their normal community controls in their psychological profile, those seeking help are, in general, different. Many have clear evidence of depression, anxiety, personality disorder, somatization. In some, their psychological problems go back to childhood and a history of abuse, physical or sexual, adult or in childhood can be elicited by gentle empathic questioning. There is also good evidence of a lowered pain threshold in the gut of these patients. IBS patients characteristically report pain at lower levels of distension than normal when subjected to balloon inflation in the small bowel or rectum. In addition a variety of changes in motility pattern have been seen in this order; none are specific and their significance is yet to be determined.

References

1. Manning AP, Thompson WG, Heaton KW et al. Towards positive diagnosis of the irritable bowel. *Br. Med. J.* **2**,653-4 (1978).
2. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut* **45**, 43-7 (1999).
3. Mearin F, Balboa A, Badia X, Baro E, Caldwell E, Cucala M et al. Irritable bowel syndrome subtypes according to bowel habit: revisiting the alternating subtype. *Eur. J. Gastroenterol. Hepatol.* **15**(2),165-72 (2003).

4. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment. Pharmacol. Ther.* **17**,643-50 (2003).
5. Everhart JE, Renault PF. Irritable bowel syndrome in office-based practice in the United States. *Gastroenterology*. **100**,998-1005 (1991).
6. Thompson WG. Irritable bowel syndrome: prevalence, prognosis and consequences. *CMAJ* **134**,111-3 (1986).
7. Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. *Gastroenterology*. **83**,529-34 (1982).
8. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ 3rd. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am. J. Epidemiol.* **136**,165-77 (1992).
9. Kay L, Jorgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J. Intern. Med.* **236**,23-30 (1994).
10. Sandler RS, Drossman DA, Nathan HP, McKee DC. Symptom complaints and health care seeking behavior in subjects with bowel dysfunction. Gastroenterology. **87**,314-8 (1984).
11. Ruigomez A, Wallander MA, Johansson S, Garcia Rodriguez LA. One-year follow-up of newly diagnosed irritable bowel syndrome patients. *Aliment. Pharmacol. Ther.* **13**,1097-1102 (1999).
12. Woodman CL, Breen K, Noyes R Jr et al. The relationship between irritable bowel syndrome and psychiatric illness : a family study. *Psychosomatics.* **39**,45-54 (1998).

Chapter 7b

TRAVELLER'S DIARRHOEA

1. DEFINITION

This is a very common problem; the most frequent health problem in travellers to developing countries of whom about 1 in 3 will develop the condition. It is defined as a two fold increase in the frequency of unformed stools and the associated symptoms include abdominal cramps, nausea, bloating, urgency, fever and malaise (1). It generally begins suddenly and is generally self limited. Clinically Travellers' Diarrhoea (TD) varies greatly in intensity, is slightly more common in the young than the old and generally occurs within the first week but may occur later, even after return from overseas. The ICD 10AM Code is A04.

2. CAUSE

This is fundamentally the faecal contamination of food or drink so that strict dietary hygiene diminishes but does not abolish the risk. It is said to be without mortality but typically results in four or five loose, watery stools per day lasting three or four days (1). Risky foods include both improperly heated, cooked and uncooked, and most especially raw vegetables, raw meat, raw seafood, as well as tap water, unpasteurized milk and dairy products and unpeeled fruit. Beer, wine, hot coffee and tea are safe. The Consensus Conference also included bottled carbonated beverages but there have been reports of bottled fluids being taken from tap water with its risk. The risk is increased in scale from eating privately, in restaurants and from street vendors. The causes are pathogenic organisms gained through faecal

contamination but the pattern of pathogens varies throughout the world. The predominant organism worldwide is the *Enterpathogenic E coli* (ETEC). These organisms produce enterotoxins which may be heat labile or heat sensitive and which cause fluid secretion and diarrhoea. There are other coliforms with different traits; their significance is probably minor but the delineation of coliform type is technically difficult.

- Salmonella gastroenteritis occurs throughout the world and it is a minor contributor to TD.
- *Campylobacter jejuni*, common throughout the world accounts for a small proportion of TD.
- *V.parahaemolyticus* associated with raw or poorly cooked seafood also occurs. Other bacteria such as *Aeromonas* and *Plesiomonas* have also been incriminated.
- Viruses. Rotavirus and Norwalk virus are also associated with a small proportion.
- Protozoa. Are uncommon causes but *E.histolytica* may cause bloody diarrhoea.
- *Cryptosporidia* have also been incriminated.

3. GEOGRAPHIC FACTORS

The disease is seen throughout most of Latin America, Africa, the Middle East and Asia and to a lesser extent in southern Europe and some Caribbean Islands. There are major geographic factors which are important. In Operation Desert Storm in Kuwait, of military personnel with diarrhoea only half had a pathogen found, predominantly ETEC and *Shigella*, (especially *sonnei*) and some salmonellas with *Campylobacter* uncommon (2). In contradistinction, in military personnel in Thailand campylobacter accounted for more than half with shigella and ETEC uncommon (3). The cause of many episodes in unknown; the possible reasons include poor analytical techniques, unrecognised pathogens and the insensitive means of detection organisms such at ETEC and *Shigella*.

4. PREVENTION

There has been much debate on this, given its significance in the tourist industry and in military activities. Given that strict hygiene can reduce but not abolish this disorder two further approaches exist.

Chemoprophylaxis can take the form of bismuth preparations. In the form of bismuth subsalicylate (Denol in the US) this affords 65% protection

but it carries the disadvantage of blackening of the tongue and stools and adding a major load of salicylate to the patient with the risk of side effects and requires repeated and prolonged dosage. The alternative is antibiotic use with a high level of effectiveness and a corresponding downside of ill-effects, particularly in the production and spread of resistant organisms. The Consensus Conference (1) recommended against it, suggesting rather the use of simple agents such as anti-diarrhoeal preparations in less severe cases and restricting antibiotic use to a brief course in the unusual severe cases. The field is ripe for further comprehensive study but the logistics in such studies outside limited military operations are daunting.

References

1. Consensus Conference Travellers' Diarrhoea. *JAMA* **253**,2700-4 (1985)
2. Hyams KC, Bougeois AL, Merrell BR et al. Diarrhoeal disease during Operation Desert Storm. *N .Engl. J. Med.* **325**,1423 (1991).
3. Murphy GS, Jr, Echeuerria P, Jackson LR et al. Ciproflaxain and azithromycin - resistant Campylobacter causing traveller's diarrhoea in US troops deployed in Thailand in 1994. *Clin. Infect. Dis.* **22**,868 (1996)

Chapter 7c

FOOD POISONING/BACTERIAL INFECTIONS OF THE GUT

1. OVERVIEW

Gastrointestinal infections are rampant throughout the world, developed as well as undeveloped. For example, it is estimated that more than 200 million episodes of acute gastrointestinal infection occur annually in the U.S. originating in contaminated food in 76 million, from water in 13 million and 122 million from human to human transmission (1). Infections of the gut are caused by a multitude of organisms from viruses to protozoa but the bacteria responsible are generally gram negative organisms. Whatever the organism they are most often transmitted by infected food or water or directly from another human. Presenting a variety of symptoms complexes they are typically associated with diarrhoea and possible systemic symptoms and are often brief. The subject is a vast one and the reader is referred to specialised texts (1, 2).

The organisms responsible separate into two categories:

1. TOXIGENIC The toxins produced are of two types, either cytotonic which stimulates intracellular energy processes, or cytotoxic which produces damage to the intestinal mucosal cells. These organisms mainly affect the upper gut, do not invade the mucosa but attach themselves to it producing toxins which alter the function of the mucosal cell, often activating the adenylate cyclase system so that there is an outpouring of fluid into the gut producing watery diarrhoea without blood or mucus. Typical ones are:

- *V. Cholerae* and enterotoxigenic *E coli* (ETEC) which produce a toxin leading to diarrhoea and dehydration from failure of

absorption of salt and water and a concurrent excessive secretion of fluid in the upper gut from cells which appear normal.

- Other toxigenic types of coliforms described are enteropathogens, enteroinvasive, enterohaemorrhagic and enteroaggregative.

2. INVASIVE. These mainly affect the terminal ileum and colon and produce ulceration of the mucosa and cellular invasion, characteristically producing a bloody mucoid diarrhoea, rectal pain, fever and systemic symptoms and sometimes blood stream invasion. The major types are:

- *SHIGELLA*
- *SALMONELLA*
- *CAMPYLOBACTER*
- *YERSINIA*
- VIRAL DIARRHOEA
- ENTEROINVASIVE *E Coli*

Although the pathogenic organisms show common symptoms such as diarrhoea, there are features peculiar to organisms and their ecology which help to distinguish them.

- *SHIGELLA* organisms characteristically produce dysentery, that is diarrhoea with blood and pus of acute onset, rectal pain and fever and systemic symptoms with abdominal pain. The disease is associated with disruption and poor hygiene and is common in war situations accounting for about 10-20% of diarrhoea around the world. It is transmitted by the faecal-oral route, relatively few organisms are necessary to create disease and, strangely, 1 in 4 volunteers fed the organism do not develop the disease. It is mostly seen in children from six months to five years. Shigella organisms produce one of the most contagious forms of GI infection. The only natural host is man, like *Salmonella typhi* and spread from man to man, or more often child to child. The infective dose is low, so that the disease spreads rapidly, not only in families but in institutions and day care centres.
- *SALMONELLA* infections are widespread, increasing and transmitted by the five Fs "flies, food, fingers, faeces and fomites". The organisms are widespread in nature inhabiting animals from sheep to fleas but particularly poultry; food contaminated in preparation is important in transmission. One of this genus, salmonella typhi produces typhoid fever which is rather different in many respects. Several syndromes are seen but the most frequent is diarrhoea lasting several days, preceded by nausea and vomiting. Salmonella organisms, particularly *S.typhi* tend to invade the blood stream and may localise in various organs.
- On the other hand there are *HALOPHILIC BACTERIA* such as *V. parahaemolyticus* which live in seawater and which can be transmitted by infected shellfish.

- *CAMPYLOBACTER* are generally transmitted from poultry, meat, dairy products and water and mostly occur in sporadic cases. Massive outbreaks are unusual, partly because it does not replicate in food and is not very contagious. It is, in western societies, now the major bacterial cause of gastroenteritis.
- *YERSINIA* enterocolitis causes a variety of syndromes from acute gastroenteritis to an invasive enterocolitis predominantly effecting children. It is most often reported from Northern Europe and Scandinavia. Widespread in animals it may enter the blood stream when immunity is compromised.
- VIRAL DIARRHOEA is a major cause gastroenteritis in the world being responsible to 30-40% of cases. The pathogens fit into four classes:
  - *ROTAVIRUS* This is responsible for about one third of hospitalised gastroenteritis in childhood, principally affecting infants of three to fifteen months of age.
  - *CALICIVIRUS* These are especially seen in day care centres; major representatives are the Norwalk and Norwalk-like viruses. These occur in all ages except infants. Shellfish are a frequent source as is the faecal-oral route but typically it causes explosive outbreaks in nursing homes, cruise ships, schools and military camps.
  - *ENTERIC ADENOVIRUS* This is generally a nosocomial infection.
  - *ASTROVIRUS* This is an organism of low infectivity, infecting children aged less than six months and often occurring in day care centres.

Three protozoa require mention:

- *CRYPTOSPORIDIA* These unicellular organisms are generally conveyed in drinking water from which it is difficult to eradicate them but its transmission, especially from infected children, readily takes place e.g. in children in day care centres and schools.
- *GIARDIA* In the west this is especially seen in children in day care centres where it is readily spread not only to other children but to adults, especially young women. It is also seen in homosexual men.
- *ENTAMOEBA HISTOLYTICA* This is largely a water borne infection, following faecal contamination.

References

1. Musher DM, Musher DL. Contagious acute gastrointestinal infection. *N. Engl. J. Med.* **351**,2417-27 (2004).
2. Hamer DL, Gorbach SL. Infectious diarrhoea and bacterial food poisoning In : Feldman M, Friedman LS, Sleisinger MH eds. *Sleisinger and Fordtran's Gastrointestinal and Liver Disease. Pathophysiology / Diagnosis / Management.* 7th Edn. (W B Saunders, Philadelphia, 2002).

Chapter 7d

PARASITIC DISEASES OF THE GUT

1. OVERVIEW

There is an awesome array of parasites that may infest humans. In the lesser developed parts of the world with poverty, malnutrition, poor sanitation and unclean water supplies they are legion. In addition they are also seen in the developed world, particularly where there is the potential for person to person transfer as in day care centers, among the rural poor and with those with impaired immunity. It is not intended to attempt to cover such an enormous field comprehensively but a brief overview emphasising the epidemiological aspects is in order. Although the organisms are numerous they may be considered under several categories which often share characteristics.

These, wide spread geographically may be considered under several headings. Extensive references are provided in standard texts (1). Gut parasites may be:

- Extra cellular
  - *Giardia lamblia*
  - *Blastocystis hominis*
  - *Entamobea histolytica*
- Intra cellular
  - *Cryptosporidium parvum*
  - *Cyclospora cayetanenis*
  - *Isospora belli*

The most frequent of these are *Giardia lamblia* and *Blastocystis*. *Cryptosporidia* may be underestimated because special processes are needed

to identify the parasite. *Blastocystis hominis* is frequently found but its pathogenicity is controversial.

2. ENTAMOBEA HISTOLYTICA

This is an important pathogen in its morbidity and its mortality and only malaria and schistosomiasis produce more deaths. Its lethal nature is partly due to its capacity to invade the body, generally producing an abscess in the liver, although its major importance is in the colon where it may produce ulceration, even mimicking inflammatory bowel disease. The consequences of this may be catastrophic in patients thought to have ulcerative colitis and given high dose steroids. Suspected for decades, it is now clear that there are two microscopically indistinguishable species; *E.histolytica* and *E.dispar*, the latter being quite benign but much more frequent than *E.histolytica* in the asymptomatic. Both organisms are widespread throughout the tropical world being readily spread through faecal contamination of water supplies and food. The role of immunity development to them is unclear.

Epidemiology

E.histolytica is wide spread, as noted, in the tropics but it occurs occasionally in the developed world, largely in groups such as immigrants, travellers and inmates in mental institutions and in sexually active homosexual males. Although traditionally amebic infection is associated with dysentery, recent studies of Bangladeshi children show that nearly half were newly infected annually but only a tiny minority developed dysentery.

3. GIARDIA LAMBIA

This organism has an extraordinarily wide distribution, being reported to infect up to 5% of people in the developed world and around 1 in 4 persons in undeveloped countries. In the developed world it is seen predominantly in young children, especially in day care centers where the colonization rate may reach 90%, in travellers, those dependant upon infected water supplies and in homosexual males.

Epidemiology

Transmission is mainly through infected water subject to faecal contamination and the relative resistance of the encysted form to chlorination renders the process inadequate and the faecal-food-oral route does occur. There is evidence that it is a zoonosis, carrier unknown. The

organism mainly infects the small bowel and may produce a rather characteristic low grade fatty diarrhea which may be prolonged.

4. BLASTOCYSTIS HOMINIS

The role of this very common organism is controversial. It may be that it acts in cooperation with known pathogens and its role as a sole pathogen in the immuno competent may be negligible.

5. DIENTAMOBA FRAGILIS

The role of this is unclear; it may produce mild abdominal symptoms and be associated with pin worm infestation.

6. CRYPTOSPORIDIA /ISOSPORA BELLI

May cause an acute diarrhoeal illness in the immuno competent but the AIDS epidemic has brought them into prominence; in the immuno suppressed they are capable of producing a chronic debilitating diarrhoea, virtually impossible to eradicate in cryptosporidiosis.

7. CRYPTOSPORIDUM PARVUM

Recognised for decades as a wide spread infection in all mammals, it is only since the AIDS epidemic that it has become recognised as a serious and frequent pathogen in humans, even the immuno competent.

Epidemiology

This organism is transmitted by cysts liberated in the intestine, particularly in farm animals or humans, by means of food, water or person to person contact with faecal-oral or sexual contact. Serological studies show evidence of infection in up to one third of well people in the developed world, particularly in those in contact with farm animals and up to 90% in the lesser developed world. The organism is relatively resistant to chlorination and so outbreaks, which may be massive, are associated with breakdown in water treatment practice, swimming pools and, once again, day-care centers. The infection may be life threatening in the immunocompromised such as in untreated AIDS.

8. CYCLOSPORA CAYETANENIS

Only recent recognised, this organism is worldwide in distribution but seen especially in the lesser developed world. Transferred by food principally or water, it seems to be common in AIDS patients in the lesser developed world. In the immunocompetent, after some weeks of diarrhoea the infection spontaneously resolves.

9. HELMINTHS

Worms are not, in most situations, a major health burden in western type societies. In the undeveloped world, given their usual faecal-oral mode of transmission, they are frequent and a potent cause of morbidity and some mortality. They are sub divided into three different types:

- Round worms (*Nematodes*)
- Flat worms – *Cestodes* (tape worms)
- *Trematodes* (flukes)

The clinical significance of this sub division is that the members of each group share major similarities in terms of life cycle, therapy and metabolism. The morbidity of these worms depends in general on the worm load and it is now evident that there are major genetic determinants of susceptibility. Details of their complex lifestyles and human impact are found in major texts (2, 3), however a brief overview is appropriate.

9.1 *Nematodes* (Round Worms)

These flourish in areas with primitive sanitation when environmental faecal contamination flourishes. Three general sorts of life cycle are recognised.

Ingestion of ova is followed by liberation of larvae into the intestine where the worms spend their lifetime. *Trichuris trichiura* and *Enterobius vermicularis* are examples.

Ingestion of ova followed by passage through the gut wall to the venous system to the lungs, alveoli, up the bronchi and then via the pharynx to the gut – *Ascaris lumbricoides*.

Penetration of the skin e.g. of bare feet and then passage through the venous system to the lungs, up the bronchi and back into the intestine – *Strongyloides stercoralis*.

9.1.1 Trichuris trichiura

These thrive in moist shaded temperate or tropical areas where there is faecal contamination of soil. Light infestations are asymptomatic. Heavy infestations of the colon are mostly seen in children leading to anaemia and growth retardation.

9.1.2 *Enterobius vermicularis* (thread worm)

This is very common in temperate as well as tropical areas and is mainly seen in school age children. The worm has a brief life for weeks and is characterised by the female worm emerging at night to lay eggs in the perianal area. Spread is facilitated by inadequate hygiene and is often intra familial.

9.1.3 Ascaris lumbricoides

Reaching up to 40cm in length, this worm is both important and prevalent throughout the world except in cold or arid climates. The female produces up to 200 000 eggs daily, hence the absolute need for adequate sanitation. Infection may be fatal but infestations are mainly seen in children. The numerous complications range from pulmonary symptoms from worm migration, abdominal symptoms, growth retardation and even intestinal obstruction from a worm bolus.

9.1.4 Strongyloides stercoralis

This is endemic throughout the tropical areas of Africa, Asia, Latin America and part of Europe and the US. It has several unusual characteristics. It is the only worm capable of completing the life cycle within the soil and the eggs hatch within the intestine so that auto infection takes place. Partly for this reason, in those infected e.g. in tropical war conditions, the infection may persist for years. This is important for the immuno suppressed or those on steroids, hyperinfection may occur with fatal results but strangely, HIV infection is not as dangerous as might be expected and cyclosporine, a potent immunosuppressant is benign in this context.

9.2 *Cestodes* (tape worms)

There are several genera of these infesting man; all have a most complex lifestyle including sojourns in different hosts, vertebrate and invertebrate as well as man. Infection takes place from eating inadequately cooked meat

(cattle or other herbivores) (*T Saginata* or *T Solium*). Biologically the necessity for human residence as part of the life cycle with contamination of animal food by human faeces attests to the long association of humans and these worms.

References

1. Li E, Stanley SL. Parasitic diseases : protozoa. In : Yamada T, Alpers DH, Kaplowicz N, Laine L, Owyang E, Powell DW eds. *Textbook of Gastroenterology* 4th Ed..(Lippincott Williams and Wilkins, Philadelphia, 2003), Vol. 2, pp. 2589-2607.
2. Pearson RD. Parasite diseases : helminthes. In : Yamada T, Alpers DH, Kaplowicz N, Laine L, Owyang E, Powell DW eds. *Textbook of Gastroenterology* 4th Ed (Lippincott Williams and Wilkins, Philadelphia, 2003) Vol. 2, pp. 2608-2625.
3. Guerrant RL, Walker DH, Weller P. *Tropical Infectious Diseases : Principles, Pathogens and Practice.* (Churchill Livingstone, Philadelphia, 1999).

Chapter 7e

ACUTE APPENDICITIS

1. DEFINITION AND OVERVIEW

Acute appendicitis, as its name indicates, is an acute inflammation of the vermiform appendix, a vestigial organ of uncertain significance. However, the significance of an acute inflammatory process there is considerable; the operation of appendicectomy (appendectomy in the US) is the most frequent of all urgent abdominal operations. Its ICD 10AM Code is K35.

Although there are isolated reports of fatal inflammation in the caecal region dating back five centuries, recognition of acute appendicitis as a clinical entity is attributed to Reginald Fitz who in 1886 reported five cases of "perforating inflammation of the vermiform appendix" shortly after which Charles McBurney delineated the clinical features including the critical feature of tenderness in the right iliac fossa at the point that bears his name to this day.

2. DESCRIPTIVE EPIDEMIOLOGY

2.1 Incidence and Prevalence

During the first half of the 20th Century it seems that the incidence rose, particularly in Europe, North America and Australasia so that up to 16% of population had an appendicectomy but in the latter three decades of the century, its incidence has fallen. For example, in England and Wales the number of appendicectomies has fallen from 113,000 in 1966 to 48,000 in 1990 (1). On the other hand its incidence in developing countries is rising

from a near zero level. Burkitt in an experience of 20 years in African mission hospitals around 40 years ago indicated its near absence in African tribal people but no such contemporary change in whites (2). In California 1983-86, the incidence of acute appendicitis in whites and Hispanics was double that of black and Asian/other groups (3) .

2.2 Risk Factors

These have been poorly investigated in contradistinction to the emphasis given to diagnosis and management. The disease is relatively rare in infants and in the elderly with a major incidence in children, adolescents and young adults (1). It is rather more frequent in males than females in whom the diagnosis is made more difficult by its confusion with gynaecological disorders.

2.3 Social class/race/occupation

There is considerable anecdotal evidence to indicate not only its rarity in primitive societies such as rural Africa in the earlier parts of 20th century and in the Himalayas where one observer noted no cases in nine years experience there. In 1939 it was reported to be eight times more common in whites than blacks in Johannesburg South Africa and all cases in blacks occurred in city dwellers in contact with western type civilization. By 1969, 200 cases in blacks were being admitted annually to Baragwanath Hospital Johannesburg (2). An urban incidence has also been reported from Germany, Rumania, Egypt and Japan. The experience of the American blacks is typical. In the first half of the 20th Century, the whites in New Orleans had four times the incidence of blacks, a ratio that had fallen to 2:1 by 1950.

2.4 Associated Diseases

Burkitt has emphasized the rarity of diverticular disease, colonic polyps and carcinoma as well as Crohn's disease and ulcerative colitis in black societies with a low incidence of appendicitis.

3. AETIOLOGY

The evidence, such as it is, strongly suggests that a dietary factor is involved, but its nature is unclear; Burkitt, who has extensively studied the

largely anecdotal evidence, makes a strong case incriminating a Western, urban, affluent diet rich in white flour and sugar rather than the high vegetable cellulose, low meat diet of most primitive societies. Studies of migrating populations - African students in Europe, Japanese migrants in Hawaii, Sudanese soldiers on British Army rations, all support this proposition. One of the most intriguing reports is from a surgeon who cared for boys in an upper class college and in an orphanage in the early part of the 20th Century. He noted a high prevalence in the cake and pastry eating college students and its rarity in the orphans (2). None of this explains the actual pathogenesis of acute appendicitis. Burkitt again has speculated on the role of a low fibre, high sucrose diet producing slower intestinal transit thus facilitating the production of the appendiceal faecoliths - pellets of inspissated faeces, calcium salts, cellular debris and bacteria, often associated with acute inflammation in the appendix. However, quantitative data from the National Health and Nutrition Survey (NHANES II) showed, in the US, a lower fibre intake in black than in whites (3). Two other hypotheses are now gaining credibility in other conditions such as IBD and |Bronchial Asthma (4). There is also some evidence of a polygenic inheritance which could explain its tendency to run in families (5).

4. NATURAL HISTORY

This is poorly documented. Whilst there is a presumption in much of the literature that acute appendicitis demands appendicectomy to prevent severe complications, it is clear that spontaneous resolution may occur. It may be that this follows the expulsion of an obstructing faecolith from the appendix allowing appendiceal drainage. Evidence for this is the finding of fibrotic appendices indicating prior inflammation and we have seen appendicitis patients giving a clear history of a prior milder attack which spontaneously resolved. Indeed, of Fitz's original 72 cases at the end of the 19th Century, the mortality rate was 26% in those not operated on although nearly all had an appendiceal abscess. By the 1970's, Massachusetts General Hospital reported one death in 246 cases of confirmed appendicitis (6).

References

1. O'Connell PR.The Vermiform Appendix. In: Russel RCG, Williams NS, Bulstrode CJK eds. *Bailey and Love's Short Practice of Surgery*. (OUP, Oxford, 2000), pp.1076-92.
2. Burkitt, DP. The aetiology of appendicitis. *Brit. J. Surg.* **58**,695-9 (1971).
3. Koepsell TD. In search of the causes of appendicitis. *Epidemiology* **2**,319-20 (1991)
4. Barker DJP. Acute appendicitis and dietary fibre : an alternative hypothesis. *BMJ* **290**,1125-7 (1985).
5. Basta M, Morton NE, Mulvihill JJ, Radovanovic Z, Radojicic C, Marinkovic D. *Am. J. Hum. Genet.* **46**,377-82 (1990).

6. Berry J(Jnr) Malt RA. Appendicitis Near its Centenary. *Ann. Surg* **200**,567-90 (1984).

Chapter 7f

RARE AND UNUSUAL SYNDROMES, POLYPOSIS SYNDROMES AND POLYPS

There are a number of rare or unusual syndromes mainly affecting the colon, some with some clinical interest, others mainly as oddities at endoscopy but of little clinical importance. It is proposed to review some of the most important or flamboyant of these entities. Why they are mainly colonic with the small intestine continuing its relative freedom from such abnormality is a topic worthy of discussion elsewhere.

1. PEUTZ-JEGHERS SYNDROME

This condition, well known to all senior medical students, is one they will probably never see in the flesh. It is due to an autosomal dominant condition characterised by hamartomas in the colon and elsewhere in the gut together with the unique perioral melanin pigmentation in nearly every patient. Multiple polyps occur anywhere in the gut, particularly the small bowel but also stomach, colon and rectum. Symptoms begin in the third decade from benign complications but by the fourth decade malignant changes affecting both GI tract and elsewhere develop. The condition is due to a defect on chromosome 19p, half the cases are familial and half apparently *de novo*. The incidence is about 1:120000 births.

2. NON NEOPLASTIC POLYPS OF THE COLON

A variety of these are seen; by definition they are benign. Their significance is mainly in their separation from polyps with malignant potential. They include:

- Hyperplastic Polyps. These are usually less than 5mm in diameter, mainly occur in the rectum, increase in number with age and remain benign.
- Inflammatory Polyps. These complicate the healing process of colonic ulceration, especially chronic ulcerative colitis but also Crohn's disease and other chronic inflammatory disorders. Unusually they may develop malignant change.
- Juvenile Polyps. These hamartomas are not unusual in children and have no malignant potential. There is also a familial form, autodominant in origin which has malignant potential.

3. SUB MUCOSAL POLYPS

These may be found in several rare situations:

- Colitis Cystica Profunda. This consists of mucus filled cysts often in the rectum resembling the standard colonic polyp but most often are a consequence of rectal prolapse or inflammatory bowel disease.
- Pneumatosis Cystoides Intestinalis. This consists of air filled cysts in the colon or small bowel producing bizarre appearances at endoscopy or radiology.

4. LAXATIVE SYNDROME

This may take two forms. The presence of either may alert the endoscopist or clinician to occult use of laxatives by the patient and clarify otherwise obscure symptom complexes.

- Melanosis Coli. This consists of a profusion of pigment laden macrophages in the mucosa to produce a strange reticulated pigmented pattern resembling alligator skin mainly in the rectum and caecum. Not rare, it follows enthusiastic use of anthroquinone laxatives – cascara, aloes, senna, rhubarb. It may appear within months and disappear as quickly on cessation of intake and be a manifestation of Munchausen's Sydrome.
- Cathartic Colon. Follows the surreptitious abuse of cathartics, generally anthroquinone types nearly always by women with psychological disturbance for many years. It involves increasing use of purges leading to an atonic colon requiring increasing laxative use and may be associated with hypokalaemia, hypovolemia and even steatorrhoea. The diagnosis is made on the radiological appearance on a atonic dilated colon resembling chronic ulcerative colitis but

with a normal colonic mucosa. It resolves in months on laxative cessation and again may be a manifestation of Munchausen's syndrome.

5. NSAIDS AND THE COLON

There is abundant evidence that NSAIDs may produce major colonic injury. It is likely the mechanism is an impairment of cyclooxygenase activity in the mucosa as in the stomach and the changes are similar. There may be occult or overt bleeding, ulceration, perforation and even perforation of diverticula and it generally occurs in older females. Furthermore there is considerable evidence that NSAIDs may produce relapse of IBD in remission generally within a week of administration. Furthermore a link of NSAIDs with collagenous colitis has been speculated upon.

6. OTHER DRUGS AND THE COLON

There are reports of colonic ischaemic changes with a number of drugs including the OCP, alosetron, cocaine and amphetamines.

Chapter 8a

BENIGN COLORECTAL NEOPLASMS - ADENOMA

1. DEFINITION

Colorectal adenoma is a benign epithelial tumour in which the cells form recognisable glandular structures and which arises in the mucous membrane of the colon. It excludes benign neoplasm of the anal canal, familial adenomatous polyposis, hyperplastic polyps, inflammatory pseudopolyps and hamartomas. The ICD 10AM Code for adenomatous polyp is D12.6.

2. DESCRIPTIVE EPIDEMIOLOGY

A colorectal polyp is a mass that protrudes into the colonic lumen. There are a number of classifications. A standard one is the division:

- tubular
- villous
- tubulovillous

There are also flat (non polypoid) adenomas described as:

- tubular, villous, villomicrotubular
- serrated
- cribriform,

but the serrated and cribriform are not universally accepted.

Adenomas form up to 75% of polyps found at colonoscopy. True adenomas, as neoplasms, all show some degree of dysplasia which may be mild, moderate or severe. More than 90% of adenomas are small, less than

1cm diameter and remain static; others (<10%) progress to adenocarcinoma in a complex transformation which seems to take 10-15 years.

Although most (adenomatous) polyps protrude into the bowel lumen, some (?<10%) are flat or depressed which makes them more difficult to recognise, which is unfortunate as they may have a greater malignant potential than the exophytic type. It is possible that the flat adenoma progresses to carcinoma through a sequence that includes a protruding polypoid lesion.

Polyps are frequent; in western societies their prevalence is much greater than in the less developed societies. A more recently recognised entity is the serrated adenoma, a flat lesion with histological features combining characteristics of hyperplastic and adenomatous polyps with genetic alteration suggesting malignant potential.

3. EPIDEMIOLOGY

The autopsy prevalence in western populations is 30-40% overall in those aged 60 or more and is greater in males. It increases with age, as does the proximal prevalence. The epidemiology of adenoma resembles that of adenocarcinoma in that the prevalence of polyps in a society mirrors that of adenocarcinoma.

Adenomatous polyps arise in an area of epithelial cell hyperproliferation and crypt dysplasia consequent upon genetic alterations. The sequence to carcinoma, should it occur, takes place in multiple steps which involve alterations in tumour suppressor genes and occupies 10-15 years (1). The natural history is difficult to study but it is evident that the epidemiology of polyps differs significantly from that of adenocarcinoma with different risk factors, sex incidence and sub site distribution (2). The risk factors for small polyps are obscure and the contribution of polyps to adenocarcinoma is unclear. Whilst there is no doubt that some carcinomas arise in polyps, we lack the evidence that all arise in this way - epidemiological, histological and genetic data indicate that the vast majority do but there is also evidence against the polyp-carcinoma sequence.

- there are small carcinomas without evidence of polyps
- the size of polyps is not age dependant but adenocarcinoma is
- their topographic distribution varies
- their sex incidence varies

4. HYPERPLASTIC POLYPS

These, also known as metaplastic polyps, are frequent colorectal lesions generally found in the rectosigmoid area. They are small and histologically consist of elongated crypts showing epithelial hyperplasia and increased branching with a slowing of migration of cells up the crypt with some abnormal cellular differentiation. Until recently they were held to have no malignant potential and so were of little interest. Interest in them as a cancer precursor has arisen because of the possession of genetic changes also seen in colorectal cancer. Otherwise typical hyperplastic polyps may also show focal dysplasia - known as serrated adenomas or hyperplastic/adenomatous polyps. The follow-up studies of hyperplastic polyps are confusing - One study found that those with a hyperplastic polyp had a doubling of rate of subsequent adenocarcinoma compared with those with a clear colonoscopy at a follow up of up to 10 years (3).

There is need for further study to settle the issue.

5. RISK FACTORS FOR ADENOMATOUS POLYP

5.1 Diet

The major variation in CRC incidence between countries, the changes seen in migrant populations and within countries all suggest major environmental influences, especially diet. A similar argument applies to Adenomatous polyposis but few good data exist (4). Adenoma prevention trials have in general been consistent in showing some benefit from Vitamin C with or without vitamin E and no benefit from beta carotene, increased fibre or diminished fat intake, remembering the problems inherent in such trials.

5.2 Dietary Fat

There are no data on per capita dietary fat intake and adenoma frequency in population studies. However there is a case control study of some interest. A comparison of 516 patients with adenomatous polyps and 551 controls without polyps on sigmoidoscopy including a detailed food frequency questionnaire focussed on partially hydrogenated vegetables oils. In the category of sweetened baked goods, a significant source of these fats, for those consuming >350kcal/day of fat the adjusted OR was 2.1 (1.3-3.5) compared with those on <50kcal/day but after adjustment for multiple

factors there was no association of total fatty acids and adenoma prevalence (5).

5.3 Dairy Products

Of more than 40 reports of colon cancer and adenoma few have found positive association with fats (6).

5.4 Meat

The role of red meat has been questioned but essentially, in spite of nearly a dozen studies the data are as soft as the conclusions. The method of cooking meat and the role of heterocyclic amines (known carcinogens) produced by meat cooked at high temperatures has received a lot of attention. A link with high temperature cooked meat has been suggested which has some laboratory support.

5.5 Fibre

Four cohort studies of bran supplementation have shown no benefit (7) as do studies including the Nurses Health Study of 88,757 women.

5.6 Fruit and Vegetables

There is evidence, regarded as not persuasive, for a protective effect of fruit and vegetables in the diet (8).

5.7 Heredity

There is a near doubling of risk in those with a family history of adenomatous polyp .

References

1. Winawer SJ. The natural history of colorectal cancer. *Am. J. Med.* **106**(A),35-65 (1999).
2. Hill MJ, Davies DJ, Giacosa A. Should we change our dietary advice on cancer preventions?
   Eur. J. Cancer Prev. **10**,1-6 (2001).
3. Huang EH, Whelan RL, Gleason N R et al. Increased evidence of colorectal adenomas in follow-up evaluation of patients with newly diagnosed hyperplastic polyps. *Surg. Endosc.* **15**,646-8 (2001).
4. Kim EC, Lance P. Colorectal polyps and their relationship to cancer. *Gastroenterol. Clin. North Am*. **26**,1-17 (1997).

5. McKelvey W, Greenland S, Chen MJ et al. A case control study of colorectal adenomatous polyps and consumption of foods containing partially hydrogenated oils. *Cancer Epidemiol. Biomarkers Prev*. **8**,519-24 (1999).
6. Giovannucci E, Goldin B. The role of fat and fatty acids, and total energy intake in colorectal cancer. *Am. J. Clin. Nutr.* **66**,1564S-1517S (1997).
7. Sengupta S, Tjandra JJ, Gibson PD. Dietary fibre and colorectal neoplasm. *Dis. Colon Rectum* **44**,1016-33 (2001).
8. Kim YI. Vegetables, fruits and colorectal cancer risk. *Nutr. Rev.* **59**,394-8 (2001).

Chapter 8b

MALIGNANT COLORECTAL NEOPLASM - CARCINOMA

1. DEFINITION

Carcinoma of the colon is a malignant neoplasm arising from the epithelial cells lining the colon. ICD 10AM Code C18 concerns the colon from the ileocaecal region to the rectosigmoid junction. It may for epidemiological purposes be distinguished from carcinoma of the rectum ICD 10AM C20 and this distinction is justified on the basis that there is some evidence of differing aetiological bases for the two. C19 is the code for carcinoma of the rectosigmoid junction. These carcinomas are generally considered to arise in adenomatous polyps. The frequency at which the transformation takes place is indeterminate but must be low and is considered to be slow.

2. DESCRIPTIVE EPIDEMIOLOGY

Colorectal cancer (CRC) collectively is among the most frequent cancers seen in western society apart from cutaneous lesions and in general second after bronchogenic carcinoma in males and breast cancer in females. Thus overall it is one of the leading internal cancers in affluent society; its incidence worldwide has greatly increased since 1975. The prevalence is the same in males and females and varies widely in western societies by a ratio of 15 to 25 to 1 with the highest rates in North America and Australasia followed by Northern and Western Europe. In high incidence societies the age standardised incidence is about $50/10^5$, the highest in males in 1990

being $53.48/10^5$ in Hawaiian Japanese followed by New Zealand non Maoris at $51.3/10^5$; In females the highest incidence is $49/10^5$ in the Yukon. In general there is good evidence of lifestyle factors in causation with a genetic basis in a small minority of cases. People moving from a low incidence to a high incidence area soon acquire the incidence of their new lifestyle and environment.

Among the epidemiological puzzles is the greater variation in incidence in the right colon than in the left colon and rectum and a shift in recent times to a higher frequency of left sided lesions.

3. TUMORIGENESIS

It is generally held that colorectal cancer arises from a series of genetic changes involving the epithelium; no particular gene is implicated but there are a succession of changes in genes controlling cell growth and differentiation, tumour suppressor genes and proto-oncogenes. This leads to a change from normal epithelium through to adenoma and then carcinoma. Recent work suggests that a factor of inherent genetic instability may sometimes be important.

4. RISK FACTORS

4.1 Heredity. (1, 1a)

About 5% of colorectal cancers are due to recognised genetic disorders. The principal syndromes are; - (Table 3).

4.1.1 Familial Adenomatous Polyposis Syndrome(FAPS) (previously called Polyposis Coli).

This only accounts for fewer than 1% of colorectal cancer. It is due to a dominant gene with a mutation of the tumour suppressor gene on chromosome 5 with high penetrance. It is characterised by the early development of numerous tubulovillous adenomatous polyps, defined by > 100 with intervening microscopic adenomas. These have nearly always developed by age 40; indeed the mean age at death is in the 30s with malignant transformation of polyps inevitable with a lag period of 10-20 years. Carriers of the gene are subject to tumours elsewhere - principally duodenal adenomas, cerebral and thyroid tumours, medulloblastomas and

desmoid tumours. In the presence of extra-colonic manifestations it is called Gardner's Syndrome; Turcot's Syndrome has polyposis coli + CNS tumour.

4.1.2 Hereditary non polyposis colon cancer. (HNPCC): Lynch Syndrome.

This is the cause of 1-5% of CRC and due to germline defects in DNA mismatch repair enzymes. Clinically it is defined by the presence of: a) at least three cases in relatives, one of whom must be a first degree relative of the others, b) one relative must have developed CRC below the age of 50, c) CRC must appear in at least two generations

4.1.3 Rarer hereditary causes are:

- Attenuated Familial Adenomatous Polyposis Syndrome (AFAP), Hereditary flat adenoma syndrome (HFAS) and Peutz - Jegher Syndromes. (Table 3)
- Non genetic aetiological factors
- Polyps: - tubulovillous adenomatous polyps

Table 3. Hereditary polyposis syndromes.

	AFAP	AFAP/HFAS	HNPCC/Lynch
Mean age at diagnosis (years)	32-39	45-55	42-49
Distribution	Random	Mainly R colon	Mainly R colon
No of Polyps	>100	<99	1
M:F	1:1	1:1	1.5:1
Other Tumours	Gastric hamartoma duodenal and small bowel polyps	Duodenal adenomas	"Cancer family syndrome"

These are very common and their prevalence rises with age. It is generally held that the overwhelming majority of cancers originate in adenomatous polyps; the other common form of polyp, the hyperplastic polyp was until recently regarded as having no malignant potential but there is now some evidence otherwise. The adenoma - carcinoma sequence is

most uncommon and it seems to take 10 - 15 years if at all; in possibly <1% of polyps it takes place by a series of changes with increasing atypia and multiple changes involving multiple genes.

The natural history is poorly characterised, the risk factors poorly understood. That dietary factors are implicated is beyond doubt. The best evidence is the correlation between the CRC incidence and the dietary pattern in the relevant community; migrant groups soon acquire the CRC pattern of the host population. Beyond this the field is beset with uncertainties. Three candidates, fat and red meat in causation and vegetable constituents of diet, particularly fibre, as protective agents all have a claim. In the 1990's there was a deluge of studies investigating the problem.

5. RISK AND PROTECTIVE FACTORS – PROVEN AND PUTATIVE

These may be considered together; for some factors it is possible that malignant and protective action are dependant upon the amount of the factor.

- Diet
  - Dietary fibre
  - Fruit and vegetable intake
  - Dietary fat
  - Red meat intake
  - Dairy products
  - Vitamins and minerals
  - Calcium and Vitamin D
- Lifestyle factors
  - Aspirin & NSAIDS
  - Smoking
  - Diabetes
  - Alcohol
  - Exercise
  - Eating frequency
  - Obesity
- Other GI diseases
  - Ulcerative colitis
  - Crohn’s disease
  - Cholecystectomy

5.1 Diet

The field has particular problems; accurate data on specific dietary components of large cohorts of people are difficult. Moreover, whilst cohort studies are capable of comprehensive and valid dietary assessments, they have the drawback of requiring prolonged follow-up. Case-control studies, on the other hand, can only measure current intake rather than that decades before and during tumour development. Meanwhile confounders have not always been considered and can be difficult to measure, especially retrospectively. A further factor confusing the topic is raised by studies of diet and polyp formation, with an assumption that polyp formation is a valid and significant precursor of cancer. Yet another factor is that foods by their nature are combinations of multiple, some probably not yet recognised, compounds and determining the significance of a single constituent poses problems. An illustration of this is Burkitt's promotion of dietary fibre as a protective factor in CRC several decades ago, based upon his extensive experience in Africa and the high fibre diet and the rarity of CRC there. A high fibre diet mandates a high intake of other nutrients of vegetable origin of which we now recognise folate and ascorbic acid as relevant. The interpretation of diet and CRC is confused by the actual plethora of studies; more than 50 case control and cohort studies up to 1993 and more since (2).

5.1.1 Dietary Fibre

Dietary fibre as a protective factor in CRC has been investigated for several decades. We now have the prospect of attempting to evaluate multiple meta-analyses. A meta-analysis in 1992 of 13 case-control studies found a consistent depression of OR to 0.53 for the highest quintile of fibre intake (P for trend <0.0001) (3). A similar OR of 0.57 was found in a similar meta-analysis (4), a study criticized on methodological grounds. More recently some cohort studies have largely negated these reports. Important large studies are typical. The Nurses Health Study, a 16 year follow up of 88,757 women showed no benefit from dietary fibre on the development of CRC (5). Terry et al followed 61,463 women for a mean of 9.6 years; cereal fibre and vegetable fibre provided no benefit (6). We must conclude that at present evidence linking dietary fibre with CRC is insecure.

5.1.2 Fruit and Vegetable Intake

These provide another confusing picture. Data are available from some of the fibre studies. A Swedish study (6) found that total fruit and vegetable consumption was inversely associated with CRC in a multivariate analysis,

mainly due to the inverse association of fruit intake with rectal CRC; for the highest quintile of fruit intake RR = 0.54 (0.33-0.89). On the contrary, Michels et al 2000 prospectively investigated two large cohorts, 88,764 in the Nurses Health Study and 47,325 men in the Health Professionals Follow-up Study (7). In 1.7 million years of follow up, no association was found between fruit and vegetable intake and CRC. A similar response was found in the Netherlands Cohort Study on Diet and Cancer (8). With studies subjected to rigorous quality evaluation, nine of ten studies examining vegetable intake found an inverse association, four other studies showed similar findings (2). The evidence for fruit is less secure (2). A key to this puzzle may be provided by the dietary content of methyl group donors, principally methionine and folate. Methylation of DNA, which may have a role in the regulation of gene expression, depends upon dietary folate and methionine, whereas alcohol is an antagonist of methyl group metabolism. In a group of 47931 cancer free male health professionals aged 40-75 followed for six years, 205 cases of colorectal cancer occurred. For >2 drinks daily versus <.25 the multivariate RR was 2.07 (1.29-3.32) and for past drinkers it was 1.95 (1.22-3.10). For the combination of high alcohol and low methionine and folate diet, the RR was 3.30 (1.58-6.88); particularly for the distal colon the RR at 7.44 (1.42-32.1) was striking. In those taking aspirin or on a high methionine or folate diet the increases were abolished (9).

A more recent study from the same group (10) reports a 12 year follow-up of 76,402 females whose dietary pattern over the years had been closely monitored. They used factor analysis to divide the dietary pattern into 'prudent' - higher in fruit, vegetables, whole grains, legumes, fish and poultry and a 'western' diet characterised by meat, refined grains, sweets, desserts and french fries. A total of 546 cases of CRC were found. After adjustment, the 'prudent' diet had a RR of 0.71 (0.50-1.00) for colon cancer where the western diet had a RR of 1.46 (.97 - 2.19), P for trend 0.02. So there was a significant association of the 'western' type diet with colon cancer, but no association of rectal cancer with dietary patterns seen.

5.1.3 Dietary Fat

Partly prompted by the Nurses Health Study (11) which demonstrated a correlation of high total or animal fat adjusted for caloric intake with CRC, fat intake achieved some prominence as a culprit. Subsequently however, none of seven large prospective studies substantiated the finding (12). In another review of 13 studies of dietary fat intake in various communities there was in 11 of the studies an association of CRC risk with total caloric intake with little if any association with fat intake independently of this (13).

5.1.4 Red Meat

Attention has also been given to a role for red meat for which there is uncertain evidence in several studies (14). Most evidence if at all points to beef but even that is controversial. The ecological evidence is not supportive eg: Japanese are eating more beef but CRC rates are falling whilst in Britain red meat consumption has fallen significantly but CRC rates have risen. Red meats tend to have associated fats and in general are expensive so their consumption has socioeconomic implications. Two recent reviews illustrate the problem. One review of 32 case control and 13 cohort studies (15) concluded that the evidence was that meat consumption is associated with a modest increase of CRC risk. On the other hand Truswell (16) cited seven further studies to counter this view and three studies of vegetarians whose RR of CRC was 0.99.

5.1.5 Dairy Products

There is some evidence of an inverse association between low fat skim milk consumption and CRC (17).

5.1.6 Vitamins

The most conclusive data come from the Nurses Health Study (18). This showed a protective effect, duration dependant, of folate. With long term (more than 15 years) use of folate containing vitamin supplements the OR fell to 0.21 (0.05-0.84) and a high dietary intake without supplements was less effective. Laboratory support for these findings comes from a group of patients with recurrent adenomatous polyps given either folate supplements or placebo; those given folate had reduced colonic mucosal cell proliferation (19). In essence the evidence strongly supports a role for dietary folate in the prevention of colon cancer. Given the fragility of the folic acid complex, as 50-95% is destroyed by cooking, and its preponderant concentration in leafy vegetables and liver, it is easy to envisage a suboptimal intake in a western type diet. Supporting data comes from a recent complex study of groups of patients with adenoma (35) CRC (28) and controls (76) subjected to detailed study including methyl group incorporation into colonic biopsy material. In short, low folate studies and DNA hypomethylation were associated with colorectal neoplasia (20).

5.1.7 Calcium and Vitamin D Intake

A large number of studies have examined the role of milk, calcium and vitamin D intake, including dietary supplementation, using cohort and case control studies. Essentially, there is inconsistent evidence for a beneficial effect of calcium and limited evidence of benefit from vitamin D. Coffee, tea and soy foods have also been examined; but no evidence of benefit is forthcoming.

In summary the evidence for diet having a major role in CRC is very strong. Although fibre, fat and red meat have raised the most interest the strongest evidence is for dietary folate, a factor which has a rational basis in the role of folate in DNA repair. If the Nurses Health Study findings are replicated then there is a powerful argument for dietary supplementation with folate. Indeed in the United States folate supplementation of breakfast cereals is mandatory. This may be a more cost effective approach to prevention of colorectal cancer than approaches such as mass screening. Likewise if the ACS findings are confirmed then smoking will also be a potent contributor.

5.2 Lifestyle Factors

5.2.1 Aspirin and NSAIDs

While various studies have suggested a prophylactic effect of aspirin and other NSAIDs on CRC development the large Nurses Health Study has helped to clarify the issue (21). Women taking four or more doses of aspirin regularly each week had a slight reduction in CRC by 10 years; by 20 years the OR was statistically significantly reduced to 0.56 (0.36-0.90). Doses higher than six weekly were no more effective and the changes were independent of other risk factors, in particular, diet.

5.2.2 Smoking

There is a vast and confusing literature on this; it is not recognised by either the Centres for Disease Control or the IARC as a cause of CRC. There is, however, an association with adenomas and some evidence of increased rectal cancer in heavy long term smokers. The best evidence is from the Physicians' Health Study (22) of a 13 year follow up. This found that after adjustment for age, sex, BMI, vegetable, fruit, alcohol, physical activity, family history, aspirin and multivitamin use, the RR for current smokers of 20+ cigarettes/day was 2.14 (1.20-3.14) with 40 pack-year smoking having a RR of 1.68 (1.20-2.31). Likewise a study from the

Swedish Twin Registry (23) found a multivariate RR of 5.3 (1.9-15.0) for current heavy smokers, largely due to an elevation of rectal cancer rate. The largest study (24) of 1,781,350 adults followed for 14 years found a significant risk for all smokers, 1.48(1.31-1.66) for 40 pack years, a risk that persisted for 20 years after cessation. They calculated an attributable risk of 12% for smoking in CRC in the US. A study (14) of 17,633 followed up for 18 years found a RR of 2.3 (0.9-5.7) in heavy smokers. On the other hand, there are a number of negative studies. In summary, the evidence for smoking as a risk factor for colorectal cancer is controversial, is only evident in large studies and is stronger for rectal cancer and not yet regarded as conclusive. It is of interest that, in contrast to the doubt concerning a smoking and CRC link, there is clear evidence of an association of smoking and adenoma.

5.2.3 Obesity

The significance of obesity as a risk factor for CRC has been extensively investigated, with differing results in males and females. There is abundant evidence for obesity as a risk factor for CRC in males (25, 26), but in females the picture is confused, with evidence of an effect in younger but not older women (27). Until recently, no study had examined the menopausal status and cancer risk but a recent study has done so with intriguing results (28). A study of 89,835 women over a mean of 10.6 years showed a near doubling of risk (hazard ratio 1.88;95%CI 1.24-2.86) of colorectal cancer in those premenopausal at entry with a BMI >30 kg/m^2, but no effect in those obese post-menopausal. The findings add to the growing evidence for the ill effect of obesity, even in the young, but no mechanism is forthcoming as yet.

5.2.4 Diabetes

There is conflicting evidence of an association between type II diabetes mellitus in females and colonic cancer, but not rectal cancer.

5.2.5 Alcohol

As noted above (see fruit and vegetables), there is good evidence for a high alcohol intake playing a role in CRC, especially in combination with a low folate and methionine diet (9). Two large cohort studies from Denmark (29) and Holland (30) have shown a dose-response relationship between total alcohol intake and rectal cancer and there are negative studies. However, the former study, extensively adjusted for other risk factors presents powerful evidence for an association with rectal cancer but, like

other studies, no association with colonic lesions. Remarkably this study shows that the association is attenuated with increasing proportion of wine as the source of alcohol.

5.2.6 Exercise

There is some evidence that strenuous physical occupational activity in males has a protective effect on rectal cancer but most studies are equivocal (31)

5.3 Other Gastrointestinal Diseases

5.3.1 CRC and Ulcerative Colitis

To understand the difficulty in evaluating this it is necessary to be aware of the slow development of our ability to diagnose ulcerative colitis (UC). Advances in diagnostic ability lead to redefinition of cases yet the evaluation of risk requires prolonged follow up. The major investigations used have been:

barium enema, the mainstay in the first half of the 20th Century, but insensitive,

rigid sigmoidoscopy, popularised in the mid 20th century, limited the view to the rectum and distal sigmoid,

rectal biopsy developed in the mid 1960's,

fibre optic colonoscopy beginning in the 1970's allowed inspection of the proximal colon,

colonoscopic biopsy became available in the mid-1980's.

A consequence of all this development of diagnostic ability has been that the earlier the series the more gross the colitis considered and the greater the obscurity in defining disease extent. Recognition has also been slow that series from specialist clinics are biased towards more serious and extensive disease with mild cases, the majority, seldom featuring in such series.

By 1970, figures of 5-10% or more at 10 years for the development of CRC were frequent. With the passage of time, the increasing use of resection for long standing and extensive disease, better treatment regimens and the growing recognition of milder cases, these figures are beginning to be revised downwards.

In general, the risk factors for CRC in UC are :

- extensive disease,
- continuous rather than relapsing disease,
- long duration,
- the presence of primary sclerosing cholangitis,

with little or no risk from proctitis or proctosigmoiditis. Given these factors, series from defined populations might be more informative.

There are at least three series claiming to represent almost all the UC patients within a defined population followed for long periods. A Danish study of 127 patients followed for up to 36 years in a population of 70,000 found only three (expected 0.13) cases of CRC limited to the 77 patients with total colitis with durations of 2, 9 and 27 years (32). A similar study from the Mayo Clinic reported 182 patients seen between 1935 and 1979. Again, three patients developed CRC (RR2.4;0.3-8.7) excluding proctitis patients (33). A large study from Copenhagen of 1161 patients seen from 1967 and followed to 1987 concerned patients with up to 40% operation rates. There were six deaths, three in patients with proctitis and three with pancolitis with a RR of 0.9 (0.14-1.4) (34). Just as in the Mayo series, life table analysis showed no deviation from expected survival. These studies really indicate that in spite of the evident morbidity, ulcerative colitis managed in a modern fashion does not carry excessive mortality overall.

Other studies, generally from hospital units, suggest cumulative rates of CRC development of about 3% at 15 years, 7% at 20 years and 12% at 25 years in patients with extensive colitis and little or no risk with left sided colitis or duration less than 10 years. (35).

5.3.2 Cholecystectomy

There is a very extensive but largely unrecognised literature on a link between cholecystectomy and subsequent CRC. A metaanalysis based upon the 95 studies up to 1996 found a small but statistically significant elevation especially for right sided tumours in women (OR 1.86:1.13-2.15) (36). More recently a large cohort study of women over 16 years found an equivocal rise for proximal lesions of 1.34 (0.97-1.88) and for rectal cancer an elevated OR 1.58 (1.05-2.30) (37). This study found no rise in distal adenoma rates. It seems clear that there is an increased risk, particularly for proximal colonic lesions, that it is more evident in women but how this links with an hypothesized disturbance of bile salt metabolism remains speculative.

5.3.3 Crohn's Disease and CRC

This carries a small but not readily quantifiable risk of CRC (38).

5.3.4 Primary Sclerosing Cholangitis

This has recently emerged as a predictive factor for CRC development. An unusual complication of UC, almost certainly with an immunological basis it is predictive with a risk of CRC of about 10% at 10 years and 32% at 20 years (39).

6. SUMMARY

In view of much current interest in screening for CRC detection and prevention it may be appropriate to conclude with recent findings for prevention. It is now evident that aspirin and at least some NSAIDS have a definite effect in impairing the development of colonic polyps. Whether this has an effect on CRC incidence with the potential for mass prophylaxis is currently indeterminate. With the large number needed to treat to prevent one carcinoma causing significant morbidity from NSAID related sideffects, it remains to be established whether the procedure has a role (40). The issue of folate supplementation, already done for breakfast cereals in the US and optional in some other countries such as Australia, both internationally and to other food sources such as flour is a topic of ongoing consideration.

References

1. Reale MA, Fearon ER. Gene defects in Colorectal Tumorigenesis. In: Young G, Rozen P, Levin B, eds. *Prevention and early detection of colorectal cancer.* (WB Saunders, London, 1996), pp. 61-86.

1a. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MN. Colorectal cancer. *Lancet* **365**,153-165 (2005).

2. Potter et al. Colon cancer: a review of the epidemiology. *Epidemiol. Rev.* **15**,499-545 (1993).

3. Howe GR, Bonito E, Castellato R et al. Dietary intake of fibre and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J. Natl. Cancer Inst.* **84**,1887-96 (1992).

4. Trock B, Lanza E, Greenwald P. Dietary fibre, vegetables and colon cancer: critical review and meta analyses of the epidemiological evidence. *J. Natl. Cancer Inst.* **82**,650-61 (1999).

5. Fuchs CS, Giovannnucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, Speizer FE, Willett WC. Dietary fibre and the risk of colorectal cancer and adenoma in women. *N. Engl. J. Med* . **340**,169-76 (1999).

6. Terry P, Giovannucci E, Michels KB et al. Fruit, vegetable, dietary fibre and the risk of colorectal cancer. *J. Natl.Cancer Inst.* **93**,525-33 (2001).

7. Michels KB, Giovannucci E, Joshipura KJ, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J. Natl. Cancer Inst.* **92**,1740-1 (2000).

8. Voorrips LE, Goldbaum RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and risks of colon cancer, rectal cancer in a prospective

cohort study. The Netherlands Cohort Study on Diet and Cancer. *Am. J. Epidemiol.* **152**,1081-92 (2000).
9. Giovannucci E, Rimm EB, Acherio A, Stampfer MF, Colditz GA, Willett WC. Alcohol, low methionine – low folate diets and risk of colon cancer in men. *J. Natl. Cancer Instit.* **87**,765-74 (1995).
10. Fung T, Hu FB, Fuchs C, Giovannucci E,, Hunter DS, Stampfer MJ et al. Major dietary patterns and the risk of colorectal cancer in women. *Arch. Intern. Med.* **163**,309-314 (2003).
11. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE, Relation of meat, fat and fibre intake to the risk of colon cancer in a prospective study in women. *N. Engl. J. Med.* **323**,1664-72 (1990).
12. Kono SA. All epidemiological evidence is important in colorectal cancer.*Br. Med. J.* **322**,611-2 (2001).
13. Howe GR, Aronson KJ, Benito E, Castelleto R, Cornee J, Duffy S et al. The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* **8**,215-8 (1997).
14. Hsing Ann W, McLaughlin JK, Chow WH, et al. Risk factors for colorectal cancer in a prospective study among US white men. *Int. J. Cancer.* **77**, 549-553 (1998).
15. Norat T, Riboli E. The role of fat, fatty acids and total energy intake in the etiology of human colorectal cancer. *Nutr. Rev.* **59**,37-47 (2001).
16. Truswell AS. Meat consumption and colorectal cancer: critique of Novat and Riboli's review. *Nutr. Rev*. **59**, 375-7 (2001).
17. Ma J, Giovannnucci E, Pollak M, Chan JM, Gaziano JM, Willett W, Stampfer MJ. Milk intake, circulatory levels of insulin - like growth factor - 1, and the risk of colorectal cancer in men. *J. Natl. Cancer Inst.* **93**,1330-6 (2001).
18. Giovannucci E, Stampfer MJ, Colditz GA. Multivitamin use, folate and colon cancer in women in the Nurses' Health Study. *Ann. Intern. Med.* **129**,517-524 (1998).
19. Khosraviani K, Weir HP, Hamilton P, Moorehead J, Williamson K. Effect of folate
supplementation on mucosal cell proliferation in high risk patients for colon cancer. *Gut* **51**,195-199 (2002)
20. Pufulete M, Al-Ghnaniem R, Leathed AJM et al. Folate status, genomic DNA hypomethylation, and the risk of colorectal adenoma and cancer: A case – control study. *Gastroenterology* **124**,1240-8 (2003).
21. Giovannucci E, Egan KM, Hunter DJ et al. Aspirin and the risk of colorectal cancer in women. *N. Eng. J. Med.* **333**,609-14(a) (1995).
22. Sturmer T, Glynn RJ, Lee IM, Hennekens CH. Lifetime cigarette smoking and colorectal cancer incidence in the Physicians' Health Study. *J. Natl. Cancer Inst.* **92**,1178-81 (2000).
23. Terry P, Ekbom A, Lichenstein P, Feyghting M, Wolk A. Long term tobacco smoking and colorectal cancer in a prospective cohort study. *Int. J .Cancer* **91**,585-7 (2001).
24. Chao A, Thun MJ, Jacobs EJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. *J. Natl. Cancer Inst.* **92**,1888-96 (2000).
25. Lew E, Garfinkel L. Variations in mortality by weight among 750 000 men and women. *J. Chronic Dis.* **32**,563-76 (1979).
26. Phillips R, Snowdon D. Dietary relationships with fatal colorectal cancer: a review of epidemiological evidence. *Nutr. Rev.* **59**,37-47 (2001).
27. Terry P, Giovannucci E, Bergquist L, Holmberg L, Wolka. Body weight and colorrectal cancer risk in a cohort of Swedish women: relation varies between age and cancer site. *Br. J .Cancer* **85**,346-9 (2001).

28. Terry PD, Miller AB, Rohan TE, Obesity and colorectal cancer risk in women. *Gut* **51**,191-4 (2002).
29. Pedersen A, Johansen C, Gronb EM. Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. *Gut* **52,**861-7 (2003).
30. Goldbohn R, Van den Brandt P, Veer P et al. Prospective study on alcohol consumption and the risk of cancer of the colon and rectum in the Netherlands. *Cancer Causes Control* **5**,95-104 (1994).
31. Nilson TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br. J. Cancer* **84**,417-22 (2001).
32. Rutegaard JN, Ahsgren LR, Janunger KG. Ulcerative colitis: colorectal cancer risk in an unselected population. *Ann. Surg.* **208**,721-4 (1988).
33. Stonnington CM, Phillips SF, Zinneisted AR, Melton LJ III. Prognosis of ulcerative colitis in a community. *Gut* **28**,1261-6 (1987).
34. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* **103**,1444-1451 (1992).
35. Lennard-Jones JE. Prevention of cancer mortality in inflammatory bowel disease in Youn GP, Rozen P, Levin P eds. *Prevention and early detection of colorectal cancer.* (WB Saunders, London 1997).
36. Read FD, Mercer PM, Harrison M, Bates T. Cholecystectomy as a risk factor for colorectal cancer: a meta-analysis. *Scand. J. Gastroenterol.* **31**,160-9 (1996).
37. Schernhammer ES, Leitzmann MF, Michaud DC et al. Cholecystectomy and the risk for developing colorectal cancer and distal colorectal adenoma. *Br. J. Cancer* **88**,79-83 (2003).
38. Gillen CD, Andres HA, Prior P, Allan RN. Crohn's disease and colorectal cancer. *Gut* **35**,651-5 (1994).
39. Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis. Evidence for increased neoplastic potential. *Hepatology* **22**,1408-8 (1995).
40. Imperiale TF. Aspirin and the prevention of colorectal cancer. *N. Engl. J. Med.* **348**,79-880 (2003).

Chapter 8c

ULCERATIVE COLITIS

1. DEFINITION

Ulcerative colitis (UC) is a worldwide, chronic, idiopathic disease of the rectal and colonic mucosa (1). The ICD 10AM code is K51. It shares many features, both in clinical picture and management, with Crohn's disease; in some patients the distinction is unclear and even hazardous. The duo is therefore often referred to as Inflammatory Bowel Disease (IBD).

2. CLINICAL PICTURE

This is generally dominated by bloody diarrhoea with or without abdominal pain; when it is limited in extent to the rectum, the diarrhoea is replaced by constipation and blood may be less evident with the passage of blood stained mucus being the outstanding symptom. The systemic effects vary from nil to a life threatening illness with fever, bloody diarrhoea, toxaemia, weight loss and dehydration. In the past such extensive disease was often fatal. However, in general the disease is characterised by chronic diarrhoea over years with periodic exacerbations maybe once a year associated with systemic symptoms of varying severity. In the form of UC localized to the rectum, haemorrhagic proctitis or ulcerative proctitis, systemic symptoms are, in general, mild and a characteristic feature is generally an unremitting course of constipation and the passage of blood stained faeces. Haemorrhagic or ulcerative proctitis may extend proximally to become a florid UC but such extension of the disorder is unusual. The disease is always most evident distally; in practice, absence of proctitis

effectively rules out the condition and favours an alternative such as Crohn's disease. If it affects the rectum and sigmoid only, as is not infrequent, this proctosigmoiditis is generally midway between the indolent picture of haemorrhagic proctitis and the more florid pancolitis. UC is associated with multiple extra colonic manifestations whose aetiology is often unclear. They range from anaemia and evidence of malnutrition and katabolism to a variety of musculo skeletal abnormalities especially large joint arthralgias and arthritis, sacroiliitis and ankylosing spondylitis and a variety of hepato-biliary disorders ranging from hepatosteatosis to cholelithiasis, biliary disease, hepatic cirrhosis and carcinoma. In long standing extensive disease, carcinoma of the colon is a significant complication.

The pathological characteristic of UC is inflammation limited to the epithelial lining of the colon and rectum and the subjacent mucosa, in contradistinction to CD where the changes extend through the thickness of the bowel wall. The histology is not specific and is characteristically that of a mucosal inflammation such as is seen in acute infective colitis.

3. DESCRIPTIVE EPIDEMIOLOGY

It affects males and females equally with an incidence in societies such as the US and Europe of 6-8/10^5 and a prevalence of 70-150/10^5. It occurs at all ages with a peak between 15 and 35 years. Despite massive research, the cause(s) of UC remains elusive although the last decade or two have seen major advances in our knowledge of risk factors and pathogenesis.

The best recognised factors are:

1. Environmental
2. Genetic

3.1 Environmental influences

These extend to a remarkable variety of factors. Basically, current thinking is that UC "results from environmental factors triggering a break down in the regulatory constraints on mucosal immuno-response to enteric bacteria in genetically susceptible individuals (1).

Among the pieces of evidence in support of this are:-

Unlike the situation in Crohn's disease for which there are major similarities, the genetic basis of UC is yet to be delineated.

- The rate of concordance for UC in monozygotic twins is only 6-14% compared with 44-50% for CD, suggesting a strong genetic component.
- A study of birth cohorts showed that the age standardized birth mortality ratio rose steadily in those born in the 19th century to a maximum in

those born about 1890 and then declined. The findings were the same in men and women and for England and Switzerland. The pattern implies that UC is strongly associated with environmental factors present in early life. The picture resembles that of DU for which there is evidence that the factor is the acquisition of H.pylori in childhood (2).

- Breastfeeding is protective against UC.
- Clear evidence of a protective effect of smoking is seen in multiple studies. Smokers have only 60% of the risk of UC of current non-smokers with heavy ex-smokers having a 4.4 fold increase of the disease. Whether nicotine is the agent concerned is quite obscure (3).
- A study of diet over the previous 5 years supplemented by adipose tissue fatty acid analysis in 43 patients with recently developed UC and 43 matched controls showed that high intake of monounsaturated, OR 3.39 (2.6-4.43) and polyunsaturated, OR 5.1 (1-26.7) fatty acids and of vitamin B6, OR 6.9 (1.6-30.7) were associated with an increased risk of UC - no other associations were found (4).
- NSAIDs administration is clearly linked with UC. An effect of COX 1 inhibitors has been noted with exacerbation after administration and for disease onset (5). There is also some evidence to implicate COX 2 inhibitors (5, 6).

There is also evidence of a social class gradient with a lower prevalence in outdoor workers (7).

The Oral Contraceptive Pill has also been linked with the development of ulcerative colitis in several studies but a meta-analysis of the nine studies showed a non-significant elevation of the OR (1.29:0.94-1.77) in users (8).

3.2 GENETIC FACTORS

That there are genetic factors is beyond dispute. Studies show a much high prevalence of UC in family members of patients than in those of controls; figures of 5-10%:1% are typical (9).

4. STRESS

As a cause, or factor in the course of the disease, this has been debated for decades. Fifty years ago considerable prominence was given to stress as a cause. With developments in the knowledge of cellular and humoral events it is now given less credence. Although psychiatric opinion had stressed the role of suppressed emotional conflict and the presence of infantile, passive and dependant types, others have pointed out the emotional effects of diarrhoea, urgency and chronic symptoms ill health. Several

studies have failed to separate UC patients from appropriate controls in these aspects. (10).

5. APPENDECTOMY

There is clear evidence that appendectomy before age 20 for appendicitis or mesenteric adenitis but not for non disease, is protective but is not protective for Crohn's disease (11), but tonsillectomy does not protect against ulcerative colitis (12). This powerful evidence for an immunological role in the aetiology remains unexplained.

6. SOCIAL FACTORS

There is evidence of a higher risk in Jews than non-Jews, in whites than Afro-Americans, in the more affluent than in outdoor workers, in users of fast food greater than twice weekly. Measles vaccination although suggested, is probably irrelevant.

7. PROGNOSTIC FACTORS

1. Extent of disease
2. Cessation of smoking
3. NSAIDs
4. Stress
5. Age at onset
6. Complications e.g. Carcinoma
7. Severity at onset

1. Proctosigmoiditis has a relatively benign course in 50% of patients and is associated with a normal life expectancy (13). In patients with left sided colitis 70% extend in 5 years to a total colitis but the survival rate is said to be normal.

For Pancolitis a major hazard is an acute onset of pancolitis with its risk of toxic megacolon, perforation and haemorrhage.

Overall the survival rate from a large Swedish survey was 80% at 20 years (14). Versus 97% in the population (15). The data indicate an improvement in outlook in recent decades. It needs to be noted that in

ulcerative colitis there is a dimished mortality rate from ischaemic heart disease, presumably due to the lowered prevalence of smoking.

2. Cessation of smoking is associated with exacerbations of the disease.

3. Administration of NSAIDs is associated with exacerbations of the disease also.

4. Age at onset. In general the younger the age of onset, the more severe the disease. Certainly this is relevant when carcinoma is considered and youth at onset is a significant predictor.

5. Stress. The role of this in controversial: sometimes it appears to provoke an attack.

6. Complications. Not only are the local complications relevant but the distant ones are also. In particular Primary Sclerosing Cholangitis indicates an increased risk of carcinoma and of 'pouchitis', in which those having a colonic resection and reconstruction develop an inflammation affecting an artificially made pouch of small bowel to produce a surrogate rectum.

In general the risk of developing carcinoma is related to total involvement of the colon, early age of onset, positive family history, more than eight years history, the presence of polyps, the presence of high grade dysplasia. The topic is addressed in Chapter 7. In those patients with an acute severe onset the course of the disease is likely top be more florid.

In summary ulcerative colitis is a disease of unknown aetiology but with strong epidemological evidence of linkage to genetic, immunological and environments factors. A unifying hypothesis is yet to emerge.

References

1. Farrell RJ, Peppercorn MA. Ulcerative Colitis. *Lancet* 359,331-40 (2002).
2. Delco A. Sonnenberg A. Military history of patients with inflammatory bowel disease : an epidemiological study among US veterans. *Am .J. Gastroenterol.* 94,679-84 (1999).
3. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig. Dis. Sciences* 34,1841-54 (1989).
4. Geerling BJ, Dagnelie PC, et al. Diet as a risk factor for the development of ulcerative colitis. *Am. J. Gastroenterol.* 95,1008-13 (2000).
5. Evans JM, McMahon AD, Murray FE, McDevitt DG, MacDonald DC. Non-steroid anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 40,616-22 (1997).
6. McCartney SA, Mitchell JA, Fairclough BD, Farthing MJ, Warner TD. Selective COX-2 inhibitors and human inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 13,1115-7 (1999).
7. Sonnenberg A. Occupational distribution of inflammatory bowel disease among German employees. *Gut* 31,1037-40 (1990).
8. Godet PG, May GR, Sutherland LD. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 37(5), 668-673 (1995).
9. Singer HC, Anderson JGD, Frischer H, Kirsner JB. Familial aspects of inflammatory bowel disease. *Gastroenteroogy.* 61,423-30 (1971)
10. Fulwood A, Drossman DA. The relationship of psychiatric illness with gastrointestinal disease. *Annu. Rev. Med.* 46,483-96 (1995).

11. Kurina LM, Goldacre MJ, Yeates D, Seagroptt V. Appendicetomy, tonsillectomy, and inflammatory bowel disease: a case-control record linkage study. *J. Epidemiol. Community Health* 56,551-4 (2002).
12. Koutroubakis IE, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a meta-analysis of published case - control studies. *Am.J. Gastroenterol.* 95,171-6 (2000).
13. Farmer RG, Easley KA, Rankin GB. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig. Dis. Sci.* 38, 1137-46 (1993).
14. Ekbom A, Helmick CG, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology* 103 (3), 954-60 (1992).
15. Perrson PG,Bernell O et al. Survival and cause-specific mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 110(5), 1339-45 (1996).

Chapter 8d

MICROSCOPIC COLITIS/LYMPHOCYTE

1. DEFINITION

Lymphocytic colitis and collagenous colitis are two unusual conditions which have only been described in the last few decades. They may be best considered under the one heading of microscopic colitis but whether they are separate diseases or parts of a spectrum of one disease remains unclear. They share many characteristics including normal colonoscopic appearances, a long term watery diarrhoea which is generally insidious in onset and a female preponderance. They both predominate in the 55 to 65 year age group and have a chronic fluctuant course but up to 95% of them may exhibit remissions. Neither has a recognised cause or satisfactory treatment. Evidence suggesting that they are separate diseases is that they differ in HLA typing. The ICD 10CM Code is K52.8. Both have been associated with a variety of autoimmune disorders but the significance of this, if any, is obscure. Incidence figures of $1\text{-}2/10^5$ for collagenous and $3/10^5$ for lymphocytic colitis are typical but studies are few (1). Histologically both are characterised by the excess of lymphocytes, plasma cells and macrophages in the lamina propria in a patchy pattern. In collagenous colitis, there is in addition, an increase in the thickness of the subepitheilial collagen layer, from the normal <4μm, it is increased to 10-100μm. Both conditions tend to remit after some years.

2. EPIDEMIOLOGY

Very little is known of this. In Europe they have been reported to have an incidence of 1-3 cases /10^5 with a prevalence of 10-16/10^5 but in elderly women the incidence may be as high as 20/10^5 p.a. There are no epidemiological data for North America. Microscopic colitis is reported to account for 10% of patients seen in referral centres for chronic diarrhoea and there the incidence is equal. There is an increased smoking rate in collagenous colitis. A Swedish study has found clear evidence of a rising incidence in both (2).

3. AETIOLOGY

This is unknown. There are claims of links to drugs, particularly NSAIDs. A link to coeliac disease has also been claimed but the data are inconclusive.

4. TREATMENT

This is equally unsatisfactory but bismuth preparations, steroids, antibiotics and bile sequestering agents have shown some evidence of benefit.

5. PROGNOSIS

The condition is not pre-malignant but apart from a tendency to remissions, the long-term natural history is yet to be described. Although the aetiology is unknown, there are puzzling links to a number of factors. An autoimmune basis is suggested by a response to steroids in some patients and a link to coeliac disease is suggested by the finding of lymphocytic colitis in 75% of coeliac patients not responding to a gluten free diet. Again, there is a link to NSAIDs use but an infective basis is suggested by the response of some patients to oral antibiotics or to bismuth subsalicylate.

References

1. Tagkalidis P, Bhathal P, Gibson P. review article : microscopic colitis. *J. Gastroenterol.* Hepatol. **17**,236-248 (2002)
2. Olesen M, Eriksson S, Bohr J, Jarnerot J, Tysk C. Micrscopic colitis : a common diarrhoeal disease. An epidemiological study in Orebro, Sweden 1993-1998. *Gut* **53**,346-350 (2004).

Chapter 8e

DIVERTICULAR DISEASE OF THE COLON

1. DEFINITION AND OVERVIEW

Diverticular disease of the colon is the most frequent disease of the colon in urbanized society. Essentially it consists of an outpouching of the colonic mucosa through the colonic wall, generally at the site of a potential defect where an arteriole passes through the wall. Diverticula are only found in the mesenteric border of the colon, the site of the blood supply. Very common, it increases in prevalence with age, reaching figures of around 50% by age 70 in western society. When present in an uncomplicated form it is termed diverticulosis attracting ICD 10AM Code is K57. There is a recent in depth review (1). Diverticulosis has unquestionably increased in prevalence in recent decades in urbanised societies. Before the mid 19th century it was a curiosity in western societies as it still is in primitive societies. Osler's Modern Medicine (1908) refers to it being found once in 2383 autopsies at Boston City Hospital. Studies have substantiated the rarity of diverticulosis in tribal societies. In Singapore it is much more frequent in Europeans than in ethnic Chinese in which it is clearly rising in prevalence as it is in recent years in urbanised communities in Africa. Diverticula predominate in the sigmoid colon and the prevalence falls of as we move proximally. Strangely, the right colon is seldom affected in western society but is reported to be the most frequent site in the East. The condition is relatively benign and it is estimated that no more than 20% of those with it will develop symptoms, possibly 1 in 200 will require hospitalization at some stage and 1 in 10000 will die of it.

2. PATHOGENESIS

This is ill understood but is most likely related to a disturbance of structure and function of the muscular coat of the colon. There is generally a thickening of the muscular wall in relation to the herniated mucosa and submucosa. The longitudinal muscle is often contracted to produce a concertina-like pattern in proximity to the diverticulosis. There is good evidence that the intraluminal pressure is raised in the affected segment (2, 3). The proposed mechanism is that the thickened wall is associated with the impaired propulsive activity and increased compliance of the wall.

3. COMPLICATIONS

The major ones are infection and inflammation – diverticulitis and bleeding.

3.1 Diverticulitis

This most often originates in one of the diverticula in the sigmoid when inspissated faecal material sets up an inflammatory process in the wall but it seldom leads to free perforation though it may well produce a peri diverticular abscess.

3.2 Bleeding.

For obscure reasons this generally originates in the right colon with a minute rupture of a vessel in an uninflamed diverticulum. Once it happens further episodes are likely, and the bleeding may be quite dramatic. Microscopic bleeding may also occur leading to an iron deficiency anaemia.

4. RISK FACTORS

4.1 Age

It is clear that the prevalence of diverticular disease rises with age.

4.2 Sex

The prevalence is equal in the sexes.

4.3 Diet

There is good evidence that the fundamental cause is the low fibre diet of affluent societies. It is much less frequent in vegetarians in the west as in people on a largely vegetable diet in the lesser developed world and there is good anecdotal and some scientific evidence of symptomatic relief with a high fibre diet.

4.4 Exercise

This is one of the most intriguing featuresf the disorders. In 47 678 American men aged 40 – 75 free of known diverticular disease, during four years of follow up 382 cases were found. After adjustment for age and energy adjusted fibre and fat intake, overall physical activity was inversely related to the risk; highest versus lowest RR=0.63(0.5-0.88), most attributable to vigorous activity. For extreme categories RR=0.60(0.41-0.87). For those who undertook no vigorous activity RR=0.93(0.67-1.69). Jogging and running combined was the only statistically significant individual activity (P trend = 0.03). For the lowest quintile of fibre intake and physical activity compared with the opposite extremes the RR was 2.65 (1.36-4.82); (4). Smoking, caffeine and alcohol intake were not associated with diverticular disease (5).

The suggestion that IBS leads to diverticulosis is unproven.

5. SUMMARY

Diverticular disease is one of the prices that mankind pays for pursuing an affluent urbanised lifestyle with clear evidence of a low fibre diet and lack of heavy physical exertion being major factors.

References

1. Stollman N, Raskin JB. Diverticular disease of the colon. *Lancet* **363**,631-9 (2004).
2. Painter NS, Truelove S. The intraluminal pressure patterns in diverticular disease of the colon. *Gut* **5**,201-3 (1964).
3. Arwidsson S, Koch N, Lehmann I, Winberg T. Pathogenesis of multiple diverticula of the sigmoid colon in diverticular disease. *Acta Chir. Scand. Suppl.* **342**,1-68 (1964).
4. Aldoori WH, Giovannucci EL, Rimm EB et al. Prospective study of physical activity and the risk of symptomatic diverticular disease in men. *Gut* **36**,276-82 (1995).
5. Aldoori WH, Giovannucci EL, Rimm EB et al. A prospective study of alcohol, smoking, caffeine, and the risk of symptomatic diverticular disease in men. *Ann. Epidemiol.* **5**,221-8 (1995).

Chapter 8f

HAEMORRHOIDS

1. DEFINITION

Haemorrhoids are varicosities of the veins of the haemorrhoidal plexus, often accompanied by inflammation, thrombosis and bleeding with ICD 10AM Codes I84,022.4 and 0.87.2. There are external, internal and mixed haemorrhoids.

- Internal haemorrhoids develop above the dentate line and so are covered by simple columnar epithelium lacking sensory innervation.
- External haemorrhoids arise below the dentate line and so are covered by stratified squamous epithelium with innervation by the inferior rectal nerve.
- Mixed haemorrhoids are confluent internal and external haemorrhoids.

Internal haemorrhoids drain via the superior rectal vein into the portal system whereas external haemorrhoids drain via the inferior rectal vein into the inferior vena cava. Haemorrhoids basically are dilated arterio venous complexes. The pathophysiology is quite obscure but although many theories have been suggested, the vascular cushion theory of the origin of haemorrhoids is the best accepted. Anatomically there are anal cushions within the submucosa of the anal canal that contain blood vessels in the form of arterioles, venules, arteriolar-venous shunts together with muscle and connective tissue. These vascular cushions at the ano-rectal junction above the dentate line are anatomically normal and are present in adults, children and even in the embryo. The best explanation is that the distal displacement of these cushions by loss or weakening of the supportive tissue leads to the production of haemorrhoids which can prolapse, bleed or thrombose.

Haemorrhoids which prolapse at the anus and are irreducible (strangulated) may create a surgical emergency.

2. FREQUENCY

They are very common; the frequency is increased among whites and in persons of high socioeconomic status and in rural dwellers and there is no sex preponderance. They are seen most commonly in young and middle aged adults but the prevalence increases with age until the sixth decade and then slightly diminishes. The prevalence of haemorrhoids varies greatly in various reports and in part depends upon the definitions employed. In Africa prevalences of about 20% and of 40% in western societies are quoted.

3. CAUSATION

The causation of haemorrhoids is not clearly understood and the data are confusing.

4. PREGNANCY

Pregnancy is well known both to initiate and aggravate the symptom of haemorrhoids particularly during labour. They may complicate 40% of pregnancies. They are less frequent after caesarean section and a large American study showed that 30% of women one month after delivery had haemorrhoids falling to 7.8% at twelve months whereas after a caesarean section the respective figures were 14% falling to 1.3%.

5. CONSTIPATION AND DIARRHOEA

A large prospective study (1) showed that constipation was not associated with haemorrhoids; Likewise, frequent laxative use was not associated. By contrast the subjective complaint of diarrhoea was significantly associated with haemorrhoids. There was a statistically significant trend with an increased haemorrhoid rate with increased frequency of diarrhoea from once per month to once per week or more. It is likely that constipation does not cause haemorrhoids but that hard stools may

traumatise haemorrhoids to cause the characteristic red arteriolar bleeding of haemorrhoids.

6. PORTAL HYPERTENSION

Although it is traditional to regard haemorrhoids as a complication of portal hypertension, recent studies distinguish haemorrhoids - enlarged vascular channels with fibromuscular tissue - from the enlarged venous channels of portal hypertension: the distinguishing features are that if compression is applied and then released, varices rapidly refill (2).

7. SPINAL CORD INJURY

There is a significant association of haemorrhoids and spinal cord injuries (3).

8. PROSTATISM

Although a link is traditional, there are no epidemiological studies in support.

9. STRAINING AT STOOL

Increased internal and sphincter tone appear to be associated with the production of haemorrhoids (4).

10. G FORCES

There is anecdotal evidence of an increased prevalence of haemorrhoids in fighter plane pilots exposed to high G forces but no objective data in support : the subject cries out for investigation.

11. PRACTICAL IMPLICATIONS

In view of the paucity of data of any scientific value on the causation of haemorrhoids apart from pregnancy little help can be offered in terms of their prevention. Particularly in view of the high frequency of haemorrhoids in the population there is a significant field open to investigation.

References

1. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation: am epidemiological study. *Gastroenterology* **98**,380-6 (1990).
2. McCormack TT, Bailey HR, Simms JM et al. Rectal varices are not piles. *Brit. J. Surg.* **171**,163 (1984).
3. Delco F, Sonnenberg A. Associations between hemorrhoids and other conditions. *Dis. Colon.* **41**,1534-42 (1998).
4. Hancock BD. Internal sphincter and the nature of haemorrhoids. *Gut* **18**,651-5 (1977).

Chapter 9a

CROHN'S DISEASE

1. DEFINITION

Crohn's disease is a chronic inflammatory disorder of the GI tract of unknown cause attracting CD 10AM Code K50. Characterised histologically by granulomata and clinically by exacerbations and remissions, the disease affects primarily the small and large intestine but it may affect the mouth rarely, and the stomach and duodenum unusually. It predominantly affects the small intestine in 30% of cases, the ileocaecal region in 60% and the colon in 10% with disease elsewhere in up to 30% of patients. A variety of extra-intestinal complications are associated, including arthritis, especially of the sacroiliac joints, uveitis and pericholangitis as well as skin disorders; their pathogenesis is unknown. In rare instances it may have extra intestinal manifestations, so called metastatic Crohn's disease. Although it was given prominence by a group including Burrill B Crohn in 1932 (1), it had been comprehensively described earlier in a little known paper by Dalziel in 1913 (2) . Whilst its prevalence in western societies has significantly increased since the 1960's, it is virtually unknown in lesser developed countries. The few cases seen in the 19th Century and recognised in retrospect were generally confused with abdominal tuberculosis. In spite of massive research, the ultimate cause of Crohn's disease is unclear but is rapidly evolving with current thought oriented to a complex interplay between environmental organisms and the subject's genetic makeup.

2. DESCRIPTIVE EPIDEMIOLOGY

2.1 Incidence and Prevalence

The disease is relatively common in North America, Europe, Scandinavia and Australia but rare in S.America, India and tropical Africa and can be difficult to diagnose with the facilities available in lesser developed countries where it can also be confused with intestinal tuberculosis. However, it seems that it has increased in frequency in recent decades in affluent societies. A British study shows a definite increase in recent years in the cohorts born in 1958 and 1970 followed to age 30. The prevalence rates at age 20 rose from 21 to $38/10^5$ (P = 0.023) (3). An increase in CD in the paediatric age group has also been reported from Stockholm with the incidence of new cases rising from $1.7/10^5$ in 1990-92 to $8.4/10^5$ in 1999-2001 (P<0.0001), with a mean age at diagnosis of 11.1 (range 2.5-15.4 years) (4). The risk to life expectancy in CD has never been quantitated until a recent cohort study of 16,550 patients with inflammatory bowel disease in the UK. For CD the loss of life expectancy was greater in the young, 5 years in those aged 15 and fell steadily in later years (5). A recent review of the North American scene illustrates some of the problems (6). Prevalence rates range from 26 to $198.5/10^5$ with incidence rates of 3.1 to $14.6/10^5$. The estimated prevalence overall in the US is between 400,000 and 600,000 of whom fewer than half require steroids at any one time. Most have a chronic remitting course, 13% an unremitting course and 10% a prolonged remission. A Canadian study from Manitoba showed an incidence of $15.6/10^5$, the same as for ulcerative colitis and the two diseases shared a significant geographic correlation (r=0.49,P<0.001). The incidence of both was higher in urban areas and was associated with higher family average income, smaller family size and it was less frequent in immigrant and aboriginal Canadians (7). Males and females are equally affected and the maximum incidence is, in general at age 15-35 with a small peak in elderly women. The disease incidence has risen but the SMR in males has fallen; it is more lethal in females and in those developing it before age 20 (8). Whilst blacks and Asians have a lower incidence, it is increased in Ashkenazi Jews. A study in Minnesota showed that the incidence rate 1940-1993 was $5.8/10^5$ with a 46% increase in incidence between 1980 and 1993 and a slightly decreased survival in those with the disease (9). There are also major differences in the incidence of Crohn's disease in Europe, varying from $9.2/10^5$ in Maastricht, Holland and Northern France to $0.9/10^5$ in North West Greece (10).

2.2 Aetiology

Numerous factors have been suggested, principally infections, as well as with cell wall deficient bacteria and viruses, genetic, familial, diet, psychological factors and immunological factors as well as measles vaccination. In general the numerous data provide little hard evidence for any of these but recent studies indicate evidence of a genetic factor related to a chromosomal abnormality in some patients.

The principal factors to be considered are:

2.2.1 Genetic

Recent studies have added greatly to our knowledge and understanding of the genetic factors in Crohn's disease. It is known that a sibling of a known case of CD has a 30 fold increase in risk. There is evidence of a mutation in NOD2 in chromosome 16 which is one locus for Crohn's disease susceptibility and there is another on chromosome 12 (11). NOD2 expression is limited to the surface of monocytes where it is thought to function as a cytosolic receptor for pathogenic components of bacteria. The genetic abnormality leads to an enhanced production of TNF α and cytokines, a characteristic feature of Crohn's disease and a response which is inhibited by corticosteroids. It is likely that lipopolysaccarides of bacterial origin through their effect on NOD2 at the monocyte cell surface leading to the production of cytokines including TNF α may explain the strong hints of a bacterial association with Crohn's disease. At least three mutations in the NOD2 gene have been identified with RR of 3.0 for heterozygotes and 23.4 for homozygotes or compound heterozygotes. These mutations were more frequent in families with only Crohn's disease and were highly associated with ileal disease (12).

Attributable Risk

It has been claimed that up to one in five cases of Crohn's disease can be attributed to NOD2 mutations and the other IBD genes yet to be discovered (13, 14, 15).

2.2.2 The Oral Contraceptive Pill (OCP)

For years there has been a strong suggestion of a link between Crohn's disease and the OCP but most studies have been small and inconclusive. A meta-analysis of reports in the English and French literature from 1975 to 1993 involved two cohort studies of 30,379 exposed and 30,673 unexposed persons and seven case control studies of 487 Crohn's disease patients, 237 ulcerative colitis patients and 3198 controls (16). An OR of 1.44 (1.12-1.86)

was found in studies adjusted for smoking. While the RR are relatively small the contribution of the OCP to the incidence of Crohn's disease is still quite significant in the group of high OCP users - young women. The use of the OCP in sexually active married women aged 15-49 varies from 36% in Australia, New Zealand and North America to 45% in Europe (17).

Attributable Risk

If the prevalence of OCP use is 50% - a conservative figure for 20 - 30 year old females and the OR is 1.4, then the attributable risk for this group becomes 0.16. The mechanism by which the OCP increases the liability to Crohn's disease is quite obscure but the consistent finding makes its effect highly likely. An Italian study (18) suggested an AR of 0.11 for the OCP.

2.2.3 Smoking

This occupies a rather similar situation to that of the OCP - a factor widespread in the community investigated by a variety of approaches in cohort and case control studies with opportunity for confounding and bias. Calkins (1989) discusses these issues in some detail and rejected 11 of the 21 studies in the literature to analyse the remaining 10, limiting the studies to case control studies with adequate data on smoking status. Ultimately 7 studies were utilized; the summary OR for current smoking compared with never smokers was 2.0 (1.65 - 2.47). An almost identical OR was found in the two excluded cohort studies (19).

Attributable Risk

The proportion of cases of Crohn's disease which may be attributed to smoking if we assume a smoking rate of 30% is 0. 23. The Italian study above (18) suggested an AR of 0.31 (.11-5.0)

2.2.4 Antibiotic Use

An emerging view is that the interaction of the gut flora with the genes governing gut defence mechanisms may be the basis of CD. Some old retrospective studies in children showed some evidence of a lack of CD with prior antibiotic use. However a recent study, free of recall bias, has compared 587 CD patients and controls adjusted for confounding. This showed that more CD patients used antibiotics ($P<0.0001$) for more courses ($P<0.001$) than their controls in the 2-5 years before CD diagnosis (OR 1.39 C.1. 1.05-1.65) (20).

2.2.5 Diet

Much attention to dietary factors has focused on the intake of sucrose. The topic was given prominence when Martini and Brandes studied 63 Crohn's disease patients and 63 controls matched for age, gender and social class. The patients consumed 177 g/day of sucrose at the time of onset of the disease, predominantly in the form of sweets and pastries, compared with the controls' intake of 74 g/day (21). Since then there has been almost a deluge of papers on the subject, virtually all confirming the excessive intake of sucrose at and before the onset of the disease (22). Moreover the issue is rendered more complex by claims and counterclaims about the significance of breakfast cereals which are frequently rich in sucrose (23, 24, 25). There is also evidence of a deficiency of fresh fruit and vegetables in the diet of CD patients (21, 26, 27) and of an increased consumption of fast foods (28). Supplementation with fish oil, a potent source of the n-3 unsaturated fatty acids eicosanoic and docosahexaenoic acid has been shown in several studies to be beneficial to CD patients. Belluzzi et al (29) gave 2.7 g of fish oil daily to 39 patients and a placebo to 39 matched controls in clinical but not biochemical remission. Over the ensuing 12 months the remission rates were 59% in patients and 26% in controls (Kaplan-Meier life table log-rank analysis P=0.006). Though strange it is consistent with our knowledge of the molecular biology. The n-3 fatty acids impair the production of leukotrine B_4 and thromboxane A_2 which are elevated in CD mucosa. They also inhibit the production of tumour necrosis factor (TNF) and interleukin 1 β. Increased production of TNF α and other cytokines characteristic of CD is inhibited also by corticosteroids, thus providing a rational basis for the effect of fish oil supplements.

2.2.6 Psychiatric/Psychological Factors

There are no good data to suggest these have a role in the initiation of CD, nor indeed of producing exacerbation. The field is characterised by small studies comparing patients with CD with controls of various types. Several studies suggest an association but evidence of directionality is lacking. In general about one third of CD patients have evidence of psychiatric disorder, predominantly anxiety and depression (30).

2.2.7 Social Factors

Although conclusive studies are lacking there is evidence of these in the development of Crohn's disease. Lack of breastfeeding had an AR of

0.11(0.01-).23) in the large Italian study (18). A US Army study showed a higher incidence in whites than non whites with a protective effect for service in Vietnam and being a prisoner of war (31). The large changes in incidence recorded in several societies are also supportive, as are the low incidence in third world countries and the social class differentials noted above. There is also strong evidence that improved childhood conditions are associated with late Crohn's disease (32). This, of course, correlates with the low prevalence in lesser developed societies and the evidence for a rising incidence over the North-South divide.

2.3 Measles Vaccination

This has been suggested as predisposing to the development of CD but several large studies have failed to support the proposition (33).

2.4 Clinical Implications

Whilst it would be logical to strongly discourage smoking, and use of the OCP with emphasis on a high fruit and vegetable diet in sufferers of Crohn's disease, no firm data are available on the value of such an approach apart from smoking in the management of established disease.

In summary we can say that about 20% of cases of Crohn's disease are attributable to genetic factors; smoking contributes about 23% and the OCP in younger women contributes about 16%. Dietary factors make an unknown but probably significant contribution. We do not know if and how much these factors act in concert; do smoking, poor diet and the OCP or gut organisms act synergistically with genetic factors?

References

1. Crohn BB, Ginsberg L, Oppenheimer GD. Regional ileitis: A pathological and clinical entity. *JAMA* 99,1323-9 (1932) .
2. Dalziel DK. Chronic interstitial enteritis. *Br. Med. J.* 1068-70 (1913).
3. Ehlin AGC, Montgomery SM, Ekbom A, Pounder RE, Wakefield AJ. Prevalence of gastrointestinal diseases in two British national birth cohorts. *Gut* 52,1117-1126 (2003).
4. Hildebrand H, Finkel Y, Grahnquist L, Lindholm J, Ekbom A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990-2001. *Gut* 59,1432-4 (2003).
5. Card T, Hubbard R, Logan RFA. Mortality in inflammatory bowel disease : a population based cohort study. *Gastroenterology* 125,1583-90 (2003).
6. Loftus EV (Jnr), Schoenfield P, Sandborn J. The epidemiology and natural history of Crohn's disease in population based patient cohorts from North America : a systematic review. *Aliment. Pharmacol. Ther.* 16,51-60 (2002).
7. Blanchard JF, Bernstein CN, Wajda A, Rawsthorne P. Small area variations and socio demographic correlates for the incidence of Crohn's disease. *Am. J. Epidemiol.* 154,328-335 (2001).

8. Weterman I, Diemond I, Pena AS. Mortality and causes of death in Crohn's disease. Review of 50 years experience in Leiden University Hospital. *Gut* 31,1387-1390 (1990)
9. Loftus EV (Jnr), Siverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Sinmeister AR. Crohn's disease in Olmstead County, Minnnesota 1940-1993 incidence, prevalence and survival. *Gastroenterology* 114,1161-8 (1998).
10. Shivananda S, Lennard-Jones J, Logan R. Incidence of inflammatory bowel disease across Europe : is there a difference between north and south? Results of the European Collaborative Study in Inflammatory Bowel Disease. *Gut* 39,690-7 (1996).
11. Hugot JP, Zouali H, Lesage S, Thomas E Etiology of the Inflammatory Disease. *Int. J. Colorectal Dis.* 14,2-9 (1999).
12. Cuthbert AP, Fisher SA, Mirza MM et al. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology* 122,867-874 (2002).
13. Hampe J, Cuthbert A, Croucher PJP et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. *Lancet* 357,1925-8 (2001).
14. van Heel DA, McGovern DPB, Jewell DB. Crohn's disease: genetic susceptibility, bacteria and innate immunity. *Lancet* 357,1902-3 (2001).
15. Elson CO. Genes, microbes and T cells - new therapeutic targets in Crohn's disease. *N. Engl. J. Med.* 346,614-6 (2002).
16. Godet PG, May GR, Sutherland LR Meta-analysis of the role of contraceptive agents in inflammatory bowel disease. *Gut* 37,668-73 (1995).
17. Oral contraceptive use worldwide. *Population Reports* xxviii(i) (nd) http://www.infoforhealth.org/pr/a9/a9suptab.shtml (accessed 04.04.2005).
18. Corrad G, Tragnone A, Caprilli R. Risk of inflammatory bowel disease attributable to smoking, oral contraceptives and breast feeding in Italy : a nationwide case cohort study. Cooperative Investigators of the Italian Group for the Study of the Colon and Rectum (GISC). *Int. J. Epidemiol.* 27,397-404 (1998).
19. Calkins B A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig. Dis. Sci*. 34,1841-54 (1989).
20. Card T, Logan RFA, Rodrigues LC, Wheeler JC. Antibiotic use and the develop of Crohn's disease. *Gut* 53,246-250 (2004).
21. Martini GA, Brandes JW. Increased consumption of refined carbohydrates in patients with Crohn's disease. *Klin.Wochenschrift*. 54,367-71 (1976).
22. Riordan AM, Ruxton CHS, Hunter JO. A review of associations between Crohn's disease and consumption of sugars. *Eur. J. Clin. Nutr.* 52,229-238(1998).
23. James AM Breakfast and Crohn's disease. *Br. Med. J.* 2,943-4 (1977).
24. Archer LNJ, Harvey R Breakfast and Crohn's disease – II. *Br .Med. J.* 2,540 (1979).
25. Rawcliffe PM, Truelove SC. Breakfast and Crohn's disease – I. *Br. Med. J.* 2,539-40(1978).
26. Kasper H, Sommer H. Dietary fibre and nutrient intake in Crohn's disease. *Am. J. Clin. Nutr.* 32,1898-1901 (1979).
27. Porro GB, Panza E. Smoking, sugar and inflammatory bowel disease. *Br. Med. J.* 291,971-2 (1985).
28. Persson PG, Ahlbom A, Hellers C. Crohn's disease and ulcerative colitis, review of dietary studies with emphasis on methodologic aspects. *Scand. J. Gastroenterol.* 22,385-9 (1987).
29. Belluzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish oil preparation on relapses in Crohn's disease. *N. Engl. J. Med.* 334,1557-60 (1996).

30. North CE, Alpers DH. A review of studies of psychiatric factors in Crohn's disease:etiologic considerations. *Ann. Clin. Psychiatry* 6,117-24 (1994).
31. Delco F, Sonnenberg N. Military history of patients with inflammatory bowel disease : an epidemiological study of US veterans. *Am. J. Gastroenterol.* 93,1957-62 (1998).
32. Feeney MA, Murphy F, Clegg AF et al. A case-control study of childhood environment risk factors for the development of childhood inflammatory bowel disease. *Eur. J. Gastroenterol. Hepatol.* 14,529-34 (2002).
33. Davis RL, Kramarz P, Bohlke K et al. Measles – mumps – rubella and other measles – containing vaccines do not increase the risk for inflammatory bowel disease : a case-control study from the Vaccine Safety Datalink project. *Arch. Pediatr. Adolesc. Med.* 155,354-9 (2001).

Chapter 9b

LYMPHOMA

1. DEFINITION

Lymphomas may be defined as solid malignancies of the lymphoid tissue. They are an important cause of morbidity and mortality, constituting the fifth most frequent cause of death from cancer in the U.S. They are subdivided into Hodgkins disease and Non Hodgkins Lymphoma (NHL). Hodgkins disease rarely affects the GI tract and will not be further considered. NHL most frequently effects and presents as a nodal problem with or without gastrointestinal involvement. We are concerned here with that minority that present with the main effect in the GI with or without local node involvement. The ICD 10AM Codes are C82 and C83.

It is not proposed to canvass the complex immunobiology of NHL. It suffices to say that NHL represents a malignant transformation of a B or T cell or rarely, another related cell in its journey from marrow or thymus to its peripheral site of activity. In the gut lymphoid tissue is called Mucosa Associated Lymphoid Tissue (MALT). Should malignant change occur then it is termed MALT lymphoma and is generally of B cell lineage. Lymphomas may occur in any part of the gut from mouth to rectum with major geographic variations. In the west, gastric lymphoma is the usual type whereas in the Middle East the small gut is usual. There are many variation, both in site and in cell of origin; their determination may be a complex problem with implications for therapy.

It is proposed to discuss briefly several of the more frequent situations.

2. GASTRIC LYMPHOMA

Gastric marginal zone B cell lymphoma of MALT type. This arises from B cells in MALT which is not normally present in the stomach but MALT tissue may appear in the stomach in response to chronic infection with H.pylori. This is generally a low grade lymphoma which usually resolves on H.pylori eradication but it may be non responsive and more aggressive. Geographically it shows major variation according to the prevalence of H.pylori colonization and the risk is calculated at 1:30000 to 1:80000 with an onset at about 60 years of age with an equal sex incidence. Almost all patients with gastric lymphoma have evidence of past or present H.pylori colonization. As the antrum is the most often affected part of the stomach, so the atrum is the usual site of gastric lymphoma but it may occur anywhere in the form of ulcer, erosive changes or erythema.

3. DIFFUSE LARGE B CELL LYMPHOMA OF STOMACH

This constitutes nearly half of gastric lymphomas. It does not have the same clear evidence of association with H.pylori but it may be a Hp related lymphoma that goes on to a high grader malignancy and dedifferentiates.

4. SMALL BOWEL LYMPHOMA

There are a variety of these based upon their different immunological characteristics. They may be of B or T cell origin. Among the larger recognised types are:

- Mediterranean Lymphoma. This is limited to the area around the Mediterranean and certain other parts such as Africa, South America and India. It occurs in young adults living in conditions of poverty and poor hygiene and sanitation. It may represent a response by MALT tissue to long standing antigenic stimulation of the gut but the situation is obscure.
- Enteropathy Associated Intestinal T Cell Lymphoma. This is a complication of Coeliac disease (Celiac Sprue in the U.S.) caused by malignant T cell transformation. It used to be regarded as a frequent complication of that disorder but it is now clear that in most wheat dependant societies, Coeliac disease is not uncommon and lymphoma is in fact a rare complication.

References

1. Collins R: Gastrointestinal lymphomas, including immunoproliferative small intestinal disease : in Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease.* 7th Ed. (Saunders, Philadelphia, 2002), Vol .1, p. 450.

Chapter 10a

ACUTE PANCREATITIS

1. DEFINITION

Acute pancreatitis is a disease characterized clinically by abdominal pain and elevated serum pancreatic enzyme levels and pathologically by acute inflammatory changes in the pancreas and varying amounts of damage to adjacent organs. The ICD 10AM Code is K85.

2. CLASSIFICATION

There are several classification systems and none are clearly satisfactory. These include:

- severity - mild
  - severe
- pathology - interstitial
  - necrotizing
- aetiology - obstructive - gall stones
  - microlithiasis
  - Sphincter of Oddi etc
- toxic - alcohol
  - drugs
  - scorpion envenomation
- metabolic - hyperlipidaemia
  - hypercalcemia
- infection - AIDS
  - mumps

- bacterial infections
- iatrogenic - ERCP
  - post operative
  - coronary bypass surgery
- autoimmune - ill understood and steroid responsive
- genetic
- trauma to the abdomen
- idiopathic – left over from when no alternative explanation available
- pancreas divisum

3. INCIDENCE

This is reported to vary from 10 to $50/10^5$ in the US but is varies widely throughout the world, principally because of variation in the prevalence of the major precipitating factors, alcohol abuse and gall stone disease. The best data come from the Oxford Record Study with hospital and death certificate data from 1963 – 1998 covering an area comprising 0.63 million in 1963 rising to 2.5 million in 1987 (1). Age standardised incidence rates doubled from $4.9/10^5$ in 1963-74 to $9.8/10^5$ in 1987-98 when standardised case mortality rates within 30 days of admission fell from 14.2% in 1963-74 to 7.6% in 1975-86 and remained fairly constant thereafter, being 6.7% in 1987-98. While around 7% died within one month of admission another 5% died between then and 12 months later, a 30 fold increase over the population rate. The rise in admission rates was mainly seen in younger males and females. Unfortunately, the study provides no data on the aetiology of the pancreatitis. It is also increasingly recognized that there are mild self limited cases which may not be recognized in statistics. The further complicating factor is that the major diagnostic tests all have significant problems in sensitivity and specificity. Additionally, save for laparotomy or autopsy, no histological diagnosis is available.

4. COURSE AND PROGNOSIS

Mild cases are self limited and almost all settle within a few days. In severe cases presenting as an abdominal catastrophe death may occur within several days or follow after a series of local and/or general complications. Mortality rates of 20-30% are the norm in the severe cases in which the galaxy of potential complications is awesome.

The evolution of acute pancreatitis into chronic pancreatitis is an important aspect. Characteristically the acute pancreatitis of alcohol abuse

has repeated episodes of decreasing severity with progressive destruction of the gland which may evolve into a syndrome of persistent unremitting pain, resistant to analgesics associated with calcified hypofunctioning gland. On the other hand the evidence is that gall stone pancreatitis does not lead to chronic pancreatitis.

5. MANAGEMENT

Apart from early stone removal from impaction at the Ampulla of Vater in appropriate cases, management is based upon alimentary rest, IV fluids and pain relief.

6. EPIDEMIOLOGY

By and large, in an affluent society such as the US the causes numerically are:

- Biliary – on third or more
- Alcohol – one third or more
- The remainder – half idiopathic, half other causes.

Biliary causes are predominantly related to gall stones. There is good evidence that obstruction by gall stones at the Ampulla of Oddi is a precipitating cause, an obstruction which can be transient; studies have shown that gall stones can be retrieved from the faeces in 30% of patients presenting with acute pancreatitis and jaundice (2). If the stone remains impacted, the pancreatitis is more severe. The link with gall stones is strengthened by the finding that cholecystectomy for stone diminished the risk of acute pancreatitis in subsequent years (3). Those with gall stones have an increased risk of acute pancreatitis which is probably 20-30% above the background but the risk remains low. In a Mayo Clinic study the risk was on 0.17% pa; hence the risk of acute pancreatitis does not justify cholecystectomy (3). It is also evident that the risk is greater the smaller the stone and there is evidence that biliary sludge may cause acute pancreatitis or even recurrent pancreatitis (4). This would explain the likelihood of acute pancreatitis in association with total parenteral nutrition, extreme weight loss, gastric surgery and some drugs such as somostatin analogues. With increasing use of endoscopic retrograde pancreatic cholangiography (ERCP), acute pancreatitis which complicates around 4% of procedures is becoming important (5).

7. SPHINCTER OF ODDI DYSFUNCTION

The role of this in acute pancreatitis is yet to be defined. A wide variety of changes – anomalous response to gut hormones, stenosis after gall stone passage, spasm of the sphincter have all been described but the difficulty and indeed the danger of cannulation of the sphincter in investigating it and the problem inherent in determining normality make for a degree of obscurity.

8. PANCREAS DIVISUM

This is a congenital anomaly leading to an abnormal drainage pattern of the ducts of the pancreas. It has been blamed for a proportion of otherwise unexplained episodes of acute pancreatitis. However, its diagnosis is difficult at Endoscopy with wide variation in the endoscopic prevalence although at autopsy its prevalence is 7% so that proof of an aetiological link with acute pancreatitis is difficult and the issue is yet to be settled. It still could be that the link depends upon the coincidence of acute pancreatitis in a patient with an already anomalous drainage system.

References

1. Goldacre MJ, Roberts SE. Hospital admission for acute pancreatitis in a English population 1963-98 : database study of incidence and mortality. *BMJ* **328**:1466-9 (2004).
2. Acosta JL, Ledesma CL. Gallstone migration as a cause for acute pancreatitis. *N.Engl. J. Med.* 290-484 (1974)
3. Moreau JA, Zinmeister AR, Melton JP, Di Magno EP. Gallstone pancreatitis and the effect of cholecystectomy : a population-based cohort study. *Mayo Clinic Proc*. **63**:466 (1988).
4. Diehl AK, Holleman DR, Chapman JB, Shwesinger WH, Kurtin WE. Gallstone size and the risk of pancreatitis. *Arch. Int. Med.* **157**:1674 (1977).
5. Christensen M, Matzen P, Schulze S, Rosenberg J. Complications of ERCP : a prospective study. *Gastrointest. Endosc.* **60**:721-31 (2004).

Chapter 10b

CHRONIC PANCREATITIS

1. DEFINITION

This is a chronic inflammatory disease of the pancreas characterized by irreversible morphological changes. It is typically associated with pain, permanent impairment of exocrine (steatorrhoea) and endocrine (diabetes mellitus) functions or both. Its ICD 10AM Codes are K86.0 and K86.1. The symptoms and signs are protean, the most outstanding being pain, steatorrhoea, diabetes mellitus, duodenal ulcer and pancreatic cancer. The prevalence of chronic pancreatitis varies widely, between 0.04% and 5% based upon autopsy studies. Few clinical studies are available. The only prospective study done in Copenhagen 1978-1979 which showed 8.2 new cases/100,000 per annum and a prevalence rate of 26.4/100,000 (1). Cross-sectional studies from Copenhagen, Stockholm, Minnesota, Zurich and Japan show incidence rates from 1 - 10/100,000 p.a. with no particular time trends. Variation may be due to differences in diagnostic rigour rather than geographical differences (2). Chronic pancreatitis is much more frequent in males.

2. DIAGNOSTIC CRITERIA

At least 2 of the following criteria must be fulfilled to make the diagnosis:

1. Clinical - abdominal pain, acute pancreatitis or alcohol abuse.
2. Functional - reduced exocrine function.

3. Morphological - calcification, pseudocyst, irregular ducts or histological evidence (3).

The disease may present as a slowly progressive, painful, entity or follow a series of episodes of acute pancreatitis, or it may be silent until fully established.

3. AETIOLOGY

Classification: A standard classification of the aetiology is the Marseilles-Rome 1998 classification (4).

3.1 CAUSES OF CHRONIC PANCREATITIS

1. Alcoholism
2. Idiopathic
3. Cystic fibrosis (in children)
4. Malnutrition (tropical pancreatitis)
5. Hereditary
6. Hyperparathyroidism
7. Obstructive chronic pancreatitis
8. Trauma
9. Pancreas Divisum
10. Ampullary stenosis

3.1.1 ALCOHOLISM

This is the cause in some 80-90% of cases in Western societies and the association of alcohol excess and chronic pancreatitis is complex (5). In contrast to alcoholic cirrhosis where there is a linear relationship between daily alcohol intake and the risk of cirrhosis (6) there is a log linear relationship between alcohol intake and the incidence of chronic pancreatitis (5). Alcohol increases the basal output of proteases, amylase and lipase (7) and an increased responsiveness of the pancreas to CCK has been reported (8, 9). It is possible that the basic mechanism is a perturbation of the intracellular transport and discharge of enzymes with consequent promotion of intracellular autodigestion together with precipitation of protein in the ducts from the high protein, low bicarbonate secretion.

There are two comprehensive controlled studies of chronic pancreatitis and alcohol; the first in Marseilles and the second an associated large multi-centre study in nine centres in France, Germany, Denmark, and Italy. (10) The findings are both remarkable and intriguing. If the daily intake of

alcohol is divided into fifteen 20g classes then the log relative risk of chronic pancreatitis rises rapidly from a zero base line to about 2 at 0 - 20 g daily and thereafter with a linear relationship rising to 6 at 260 - 280 g/day.

There is also, an association of risk with the mean daily intake of protein and of fat; the relationship between protein intake and log RR is linear with a small rise in risk with rising protein intake. For fat intake the RR is quadratic being lowest at fat intakes of 85-110g/day and higher at both lower and higher intakes, whatever the class of alcohol intake. In this study, the mean duration of alcohol use was 18 $\pm$ S.D. 11 years, with a total intake of 1166+791 litres in males. There were three males with an alcohol duration of less than three years. These and other data such as the shape of the log RR/daily intake graph suggest major variations in individual susceptibility to alcohol. There is also a very weak association with daily intake and duration of alcohol intake which further suggests a major role for individual susceptibility, an argument strengthened by the observation that only 5-10% of chronic alcoholics develop chronic pancreatitis. The practical significance of these findings is that patients with chronic pancreatitis may be at increased risk with intakes of alcohol as low as 20g or less daily and must be advised to be totally abstinent. The evidence also suggests the benefits of a normal diet of 85-110 g of fat daily with a reduction of protein intake, in view of the small but significant rise in liability to chronic pancreatitis with rising protein intake in alcoholic pancreatitis.

3.1.2 IDIOPATHIC CHRONIC PANCREATITIS

This varies in incidence, possibly due to major variations in its counterpart, alcoholic pancreatitis, or due to failure of recognition that such a condition exists. Reports of its prevalence vary from 10% - 40% of all cases. It has two types. The juvenile type predominates in males under 25 and is characterised by a long history of recurrent abdominal pain and calculus formation; steatorrhoea and diabetes mellitus appear after about a quarter century. The late form, generally seen after aged 60, often manifests as pancreatic calcification in routine abdominal x-rays, on the investigation of malabsorption syndrome or at autopsy. Microscopy shows chronic inflammatory change. (11)

It has been proposed that there is a common underlying genetic defect as the basis for most chronic pancreatitis. The development of the phenotype however may be modified by factors such as alcohol and cigarettes (12). As long suspected, it is now clear that an as yet undetermined proportion of hereditary and idiopathic pancreatitis patients have a genetic basis associated with mutations on chromosome 5 or 7(13). Moreover, several studies have shown an increased frequency to as much as 6% in the presence of a genetic

abnormality in alcoholic chronic pancreatitis also. It seems likely that several genes may be involved in a causative or permissive role in a variety of forms of chronic pancreatitis.

3.1.3 MALNUTRITION or TROPICAL PANCREATITIS

This is a hazard for impoverished people and has been reported in India, Africa and Indonesia only. Affecting males and females equally, it usually presents at about age 12 and is characterised by disseminated calcification of the pancreas with the development of insulin resistant brittle diabetes mellitus. Characteristic features are signs of malnutrition including hair and skin changes, abdominal distension and parotid enlargement. This is usually on a background of poverty and a low calorie, low protein, high carbohydrate diet. Recurrent abdominal pain in childhood, diabetes at puberty and death in the prime of life has been noted as the natural history of the disease (14). The cause is unclear; the association with protein deficiency and the very low protein tuber cassava (14) do not fully explain the syndrome.

3.1.4 HYPERPARATHYROIDISM

Though rare, this is an important factor because of the apparent response to parathyroidectomy. Although it seems likely that the pancreatitis is secondary to the elevated serum calcium and the consequent calcium deposition in the ducts, calcification is reported in only about half the patients. The condition generally occurs at about age 50. A practical trap is the frequently observed depression of the serum calcium in the acute phase which may obscure the otherwise characteristic elevation of the serum calcium in the condition. Pancreatitis is the presenting symptom in about half the cases. A diagnostic clue is the presence of pancreatic calcification in family members (15).

3.1.5 HYPERLIPIDAEMIC CHRONIC PANCREATITIS

This is a rare form of chronic pancreatitis usually associated with serum triglyceride levels above 1,000 mg % (16).

3.1.6 OBSTRUCTIVE CHRONIC PANCREATITIS

This is a rare form and is the result of obstruction to a large duct by calculi, trauma or stone and is potentially reversible by relief of the obstruction.

3.1.7 PANCREAS DIVISUM

This is a debatable cause of chronic pancreatitis attributed to failure of the ventral and dorsal buds of the embryonic pancreas to unite. It may be attributable to the coincidence of the anatomical defect and idiopathic pancreatitis.

3.1.8 RARE ASSOCIATIONS

There are a large number of rare associations in the literature. For some at least the authenticity of the linkage is debatable. These conditions include drugs (Phenytoin), Alpha 1 Antitrypsin Deficiency, Coeliac Disease, Sclerosing Cholangitis, Sjogren's Disease, Autoimmune disease, Waldenstrom's Macroglobulinamia, Haemochromatosis, Disseminated Lupus Erythematosus, trauma and previous Bilroth 2 gastrectomy (17). Recently an autoimmune pancreatitis unassociated with other recognized autoimmune disease has been proposed (18).

3.2 SMOKING

The association of chronic pancreatitis with smoking is poorly recognised. A case-controlled study of 98 patients with pancreatitis, of whom 62 had chronic pancreatitis and 451 controls showed that smoking and alcohol were independent risk factors for chronic pancreatitis (19). The finding has been replicated. The situation is clouded by the association of alcohol abuse and smoking together.

3.3 RADIATION THERAPY

There are now a small number of patients reported as developing chronic pancreatitis many years after radiotherapy to the upper abdomen (20)

3.4 INFLAMMATORY BOWEL DISEASE

A French report has presented strong evidence for an association of ulcerative colitis (12 cases) and of Crohn's disease (16 cases) with chronic pancreatitis but a relationship to prior drug therapy has not been excluded (21).

4. IMPLICATIONS FOR CLINICAL MANAGEMENT

It is essential that patients with chronic pancreatitis avoid alcohol in any dose and also smoking. There is also theoretical merit in modifying the protein and fat intake so that the protein intake is kept in the lower normal range, say , 84g/day but not so low as to create protein malnutrition. Fat intake should be kept within the range 85 - 110 g a day. In cases of acute pancreatitis where the aetiology is not entirely clear a serum calcium estimation should be done in convalescence. It is also likely that molecular biology will provide a means of evaluating the role of genetic factors in the genesis of pancreatitis where the aetiology is not clear.

It is now becoming clear that there is a genetic basis for at least some cases of idiopathic and familial pancreatitis but also some alcoholic pancreatitis (22). This is an attractive possibility to explain the strange non-linear association of alcohol in take and pancreatitis.

References

1. Copenhagen Pancreatic Study. An interim report from a prospective epidemiological multicenter study. *Scand. J. Gastroenterol.* **16**,305 (1981).
2. Worning H. Incidence and prevalence of chronic pancreatitis. In: Beger HG, Buchler M, Ditschunheit H, eds. *Chronic Pancreatitis.* (Springer Verlag, Berlin,1990), p.8.
3. Pedersen NT, Worning H. Chronic Pancreatitis. *Scand. J.Gastroenterol.* **216** (Suppl.),52-8 (1996).
4. Sarles H, Adler G, Cani R et al. The Pancreatitis Classification of Marseilles - Rome 1988. *Scand. J.Gastroenterol.* **24**,641-2 (1989).
5. Durbec JP, Sarles H. Multicenter survey of the etiology of pancreatic diseases: Relationship between the relative risk of developing chronic pancreatitis and alcohol, protein and lipid consumption. *Digestion* **18**,337-50 (1978).
6. Lelbach WK. Cirrhosis in the alcoholic and the relation to the volume of alcohol abuse. *Ann. N.Y. Acad. Sci.* **252**,85 (1975)
7. Singh M, La Sure MM, Bockman DE, Pancreatic acinar cell function in rats chronically fed an ethanol diet. *Gastroenterology* **82**,425 (1982).
8. Sarles H, Tiscornia O, Palasiano G et al. Effects of chronic intragastric ethanol administration on canine exocrine pancreatic secretion. *Scand. J. Gastroenterol.***15**,241 (1980).
9. Renner IG, Rinderknecht H, Valenzuela JE et al. Studies of pancreatic secretions in chronic alcoholic subjects without pancreatic insufficiency. *Scand. J. Gastroenterol.* **15**,241 (1980).
10. Durbec JP, Sarles H. Epidemiology of chronic pancreatitis. Alcohol and dietary habits. In: Gyr KE, Singer MV, Sarles H eds. *Pancreatitis. concepts and classification.* (Excerpta Medica, Amsterdam, 1984), pp.351-3.
11. Amman RW. Chronic pancreatitis in the elderly. *Gastroenterol. Clin. North Am.* **19**,905(1990).
12. Lankisch MR, Imoto M, Laver P, Di Magno EP. The effects of small amounts of alcohol on the clinical course of chronic pancreatitis. *Mayo Clin. Proc.* **76**,242-51 (2001).

13. Pitchumoni CS. Special problems of tropical pancreatitis. *Clin.Gastroenterol.* **14**,941-59 (1984).
14. Mixter CG, Keynes WM, Cope O. Further experience with pancreatitis as a diagnostic clue to hyperparathyroidism. *N. Engl. J. Med.* **266**,265-72 (1962).
15. Cameron JL, Crisler C, Margolis et al. Acute pancreatitis with hyperlipidemia. *Surgery* **70**,53-61 (1971).
16. Pitchumoni CS. Chronic Pancreatitis. A historical and clinical sketch of the pancreas and pancreatitis. *The Gastroenterologist* **6**,24-33 (1998).
17. Yen S, Hsieh Chung-chen, MacMahon B. Consumption of alcohol and tobacco and other risk factors for pancreatitis. Am. J.Epidemiol.116,407-14 (1982).
18. Okazaki K, Chiba T. Autoimmune related pancreatitis. Gut 51,1-4 (2002).
19. Pitchumoni CS Does cigarette smoking cause chronic pancreatitis? J. Clin. Gastroenterol.31,274-5 (2000)
20. Levy P, Menzelxhiu A, Paillot B, Bretagne JF, Flejou F, Bernardes P. Abdominal radiotherapy is a cause for chronic pancreatitis. Gastroenterology 105,905-9 (1993).
21. Barthet M, Hastier P, Bernard JP et al Chronic pancreatitis and inflammatory bowel disease: true or coincidental association? Am .J.Gastroenterol .94,2142-48 (1999).

Chapter 10c

CARCINOMA OF THE PANCREAS/MALIGNANT TUMOURS

1. DEFINITION AND OVERVIEW

Adenocarcinoma is almost exclusively the malignancy affecting the pancreas. The ICD10AM code is C25. Although it is not high on the list of human malignancies, because of its almost universal fatal outcome, it has become the fourth highest cause of death in malignancies in males (1) and fifth in females. The five year survival rate is only about 1-3% in whites and 3-5% in blacks in the U.S. Both early diagnosis and adequate early resection are most unusual. It has been increasing in frequency over the last 50 years and more, for totally unexplained reasons, in western society.

2. PREVALENCE

It kills 26000 persons annually in the U.S. and has the lowest five year survival rate of any cancer. In women in the U.S. the age adjusted annual incidence $/10^5$ rose from 4.5 in the 1940s to $7.9/10^5$ in the 1980s and in men from $9.2/10^5$ in the 1940s to $12.8/10^5$ in the 1960s and then stabilised.

3. GEOGRAPHIC AND RACIAL FACTORS

Here there is considerable variation; in the U.S. blacks have a higher incidence than in whites but the highest incidence recorded is in the male New Zealand Maori of Polynesian origin.

4. RISK FACTORS

These are not well understood or indeed clarified. The major ones for which the evidence seems clear are:

- Cigarette smoking
- Previous pancreatitis
- Familial / genetic
- Aromatic amines
- Hereditary pancreatitis
- Diet
- Obesity and lack of exercise
- Previous gastric surgery
- Diabetes mellitus
- Alcohol
- Coffee
- Gall stones

4.1 Cigarette Smoking

There is now convincing evidence for smoking as a risk factor with a doubling of risk which reverts to unity after a 10-15 year abstinence. It is said that cigars and pipes are benign but no data have been sighted.

4.2 Previous Pancreatitis

The most potent study is one of VA patients in the U.S. (2) of 2639 carcinoma of the pancreas patients matched to 77774 controls. The odds ratio rose from 2.04 (1.53-2.72) in those with pancreatitis seven or more years previously to 2.31 (1.87-2.86) where the pancreatitis was at least a year before suggesting that some episodes of pancreatitis have carcinoma as a basis. In a multi variate analysis, the odds ratio was 3.42 but there was no evidence of risk with alcoholism or gall stones.

4.3 Familial / Genetic Factors

There is undoubtedly such a risk factor not yet fully explained. Of those with pancreatic carcinoma, 7-8% have a relative with it and it is estimated that familial / genetic factors account for as many as 10% of pancreatic carcinoma and several genes have been suggested. This is particularly in patients with hereditary pancreatitis where the risk is increased at least 10 times. The other group of genetic causes is in the genetic gut disorders such as MEN type 1, Gardner and Peutz-Jegher syndromes.

4.4 Aromatic Amines

These chemicals, present in tobacco smoke and in cooked meat, as well as in the chemical industry are probably causative but the mechanism and significance are yet to be resolved.

4.5 Hereditary Pancreatitis

As noted above, this is a potent factor but contributes only a small quantum to the total cases.

4.6 Obesity and Lack of Exercise

These have been clearly linked to the disorder (3). In those with a BMI of at least 30 the OR was significantly elevated to 1.72 compared to those with a BMI of less than 25. Physical activity was protective with the OR significantly reduced to 0.45 comparing the highest to the lowest level of activity but the protection did not extend to thin people with a BMI of less than 25kg/m^2.

4.7 Diet

There is some evidence that an elevated fat and meat intake increases the risk with a protective effect from fruit and vegetables.

4.8 Diabetes Mellitus

This has been raised as a risk factor but a large Italian study indicates that the risk is limited to diabetes of recent onset suggesting that the diabetes was caused by the cancer (4).

4.9 Alcohol, Coffee (5), Gall Stones

There is no firm evidence to inculpate these as causative factors.

References

1. Di Magno EP, Reber HA, Tempero HA. AGA Technical review on the epidemiology, diagnosis, and treatment of pancreatic ductal carcinoma. *Gastroenterology* **117**,1464-1484 (1999)
2. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology* **109**,247-51 (1995).
3. Michaud DC, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height and the risk of pancreatic cancer. *JAMA* **286**,921-9 (2001).
4. Gullo L, Pezzilli R, Morselli-Labate AM and the Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. *N .Engl. J.Med.* **331**:81-4 (1994)
5. Tavani A, LaVecchia C. Coffee and Cancer : a review of epidemiological studies. *Eur. J. Cancer Prev.* **4**,241-256 (2000).

Chapter 11a

HEPATITIS A

1. OVERVIEW

Hepatitis A is a widespread disease of man, of great antiquity. It is generally a fairly benign disease, never becomes chronic and apart from fatalities (±1/1000) in the acute phase, is followed by complete recovery of the liver without recognised sequelae. It is classified as ICD 10AM Code B15. Being transmitted by the faecal-oral route almost exclusively it reflects the hygienic standards of the community concerned and used to be a major cause of illness in armies in the field, figuring prominently in World War II. For example, in the lead up to the battle of Alamein in 1942, the attack rate in Australian servicemen was over nine per 1000/month but throughout the Middle East campaigns no fatalities occurred in Australian troops. In the US forces in World War II there were 200 000 cases. Generally it occurs in epidemics with a 5-20 year cycle, often peaking in late autumn and early winter in temperate climates (1). In affluent western societies epidemics are less evident but contaminated shellfish still represent a hazard. In Shanghai as recently as 1988, an epidemic from contaminated shellfish affected nearly one third of a million people. An RNA virus, it is classified as a hepatovirus with only one serotype although a number of strains exist and one attack confers lifelong immunity with persistence of IgG antibody; in adults over 70, its prevalence is 75% in the US (2). Being unusually resistant to heat, ether or acids it may persist in the environment for weeks but its infectivity, apart from faecal contamination of food or drink is low. The incubation period is about four weeks and faecal shedding occurs for about a week or so before symptoms appear and for only a few days afterwards and viraemia is quite brief, so that infectivity is largely finished by the time the disease is

evident (3). An implication of this is that once the patient has developed the florid disease there is little to be gained by strict isolation techniques as the infectivity has by now virtually passed (2). An important fact is that the infection never becomes chronic.

2. INCIDENCE AND PREVENTION

In Western Societies massive epidemics are now rare but sporadic cases and small outbreaks occur, often traceable to a food handler and intra familial spread is not unusual on account of the viral shedding before the onset of symptoms. Although the disease is markedly declining in the west it is still not uncommon; an estimated 130,000 cases occur annually in the US. In peacetime the groups at greatest risk are travellers, military personnel in endemic areas, promiscuous homosexual males and those concerned with Day Care Centres and institutions for the intellectually disabled. The infection in young children is often mild or inapparent increasing the hazard to their carers and neonatal intensive care units provide another risk. In spite of these factors health care workers overall do not have a higher incidence than others.

A literature review has provided better estimates of risk in travellers (4). The risk of symptomatic hepatitis A for a one month stay by a non-immune person in a developing country is about 3/1000. This applies to short stay visitors, even those staying in luxury hotels; for back packers and similar travellers the risk rises to 20/1000 and for stays in southern Europe the risk is 0.05-0.10/1000/month but the case fatality rate is very low at about 0.15%, rising to about 2% for those over 40 years of age. These figures can only be interpreted in the light of the age of the traveller. Data on immune status are available for Singapore, the US and Europe. The figures are dramatic and largely parallel. The hepatitis A serology positivity is only about 10% in those under 20 years old and rises steadily to about 80% in those aged 65 or more (3). So the younger age groups; the typical back packer, is also the most susceptible.

3. ETHNICITY

For US Navy and Peace Corps personnel aged 18-50 years the hepatitis A positivity rate overall is 8% but for the whites less at 5%.

4. VACCINATION

Two forms are available, active and passive. Active vaccination with a killed or attenuated virus provides excellent protection estimated to last 10-25 years if adequate dosage is given; the side effects are minimal but the product is expensive (4). A passive immunisation immunoglobulin preparation is available. It is produced from pooled plasma but given the falling antibody rates in the young its potency in the future may be expected to fall. It currently provides 85-90% protection lasting 3-5 months so it does provide protection for the holiday traveller but it too is expensive. To prevent one case of hepatitis in a traveller exposed for two weeks each 10 years would cost USD33000 for a vaccination program and USD9400 for an immunoglobulin approach (4).

5. GEOGRAPHIC AND SOCIAL FACTORS

There is an inverse relationship with socioeconomic state and a major north-south gradient in Europe with low prevalence in Scandinavia and higher one in Mediterranean countries.

Paradoxically, as the disease has become less frequent, clinical cases have become more severe. This is because in the past most cases occurred in children under the age of ten with a mild course. Now the elderly, some of whom are non-immunes, tend to have a much more aggressive course with mortality rates in the region of 1-3%. The management of the disease is supportive. There is no specific therapy; antiviral agents and steroids have no role but occasionally liver transplantation for fulminant hepatitis may be necessary.

6. SUMMARY

Hepatitis A is an infection which in primitive communities with poor hygiene is largely limited to youngsters in whom the infection is nearly always mild or inapparent providing life-long immunity. With rising living standards in populations with access to uncontaminated water, and sanitation standards to limit faecal contamination of the food chain it has become an infrequent sporatic disease often affecting older adults in whom it runs a more severe course even occasionally fatal. In environments where hygienic standards are poor such as in the undeveloped world or conditions of social unrest or war it is a significant problem and to travellers from the developed world the majority of whom are not immune. Fortunately there are no

significant sequelae and potent active and passive immunization procedures are available.

References

1. Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. *Int. Hepatology* **18** (Suppl.2),S11-14 (1993).
2. Craig AS, Schaffner W. Prevention of hepatitis A with the hepatitis A vaccine. *N. Engl. J. Med.* **350**,482-492 (2004).
3. Dienstag JG. Hepatitis A in: Bircher J, Benhamou J-P, McIntyre N, Rizetto M, Rodes J. Ed. *Oxford Textbook of Clinical Hepatology* 2nd Ed. (OUP, Oxford, 1999), pp. 870-5.
4 Steffen R, Kane MA, Shapiro CN, Bilo N, Schoelborn KJ, van Damme P. Epidemiology and prevention of hepatitis A in travellers. *JAMA* **272**,885-9 (1994).

Chapter 11b

HEPATITIS B

1. OVERVIEW

Hepatitis B is one of the at least seven viruses primarily affecting the liver in humans. One of the most frequent diseases afflicting mankind, it is estimated to affect 5% of the world population (1, 2, 3). In the undeveloped world, childhood infection is almost universal, most episodes of which are subclinical and subicteric and in one half of which there are not even abnormal liver function tests. This infection leads to complete recovery and lifelong immunity thereafter as a rule although about 1% die in a fulminant episode. However, in about 10% of episodes the infection fails to resolve and a so called 'carrier state' follows. As a consequence, the worldwide prevalence of the Hepatitis B carrier state is about 300 million. In the U.S. the carrier rate is about 1-1.25 million with serological evidence of past infection in about 6% of those less than 20 years, rising to 31% in those over 20. In general the male:female ratio is 2:1. The ICD 10AM Code is B16.

In developed countries Hepatitis B accounts for about 50% of sporadic acute hepatitis of which in the US 50% is attributable to HIV drug use, homosexual activity, transfusion and occupational causes.

2. THE VIRUS

This is a rather strange virus with a complex structure, several of whose components have been elucidated and which can be fairly readily detected as can their antibodies and a complex naming system has evolved. The principal components are:

- HBsAg : the outer coat of the virion (virus) which indicates the presence of the virus.
- HBsAb : antibody to the above.
- HBeAg : its presence indicates active viral replication.
- HBeAb : antibody to the above.

Virus in the blood can also be detected by PCR amplification. The virus is a member of the hepadnavirus family which are DNA viruses of complex structure affecting humans and a few other species focused on the liver and few other organs.

3. PREVALENCE

The prevalence of Hepatitis B infection varies widely throughout the world. In the Far East, China, S.E Asia, Philippines, Indonesia, Middle East, parts of Africa and South America carrier rates are high ranging from 8-15%. In these areas, non carriers have almost uniformly evidence of past infection. On the other hand, in areas of low prevalence such as the U.S., Canada, Northern Europe and Australia, the prevalence of chronic Hepatitis B positivity is less than 2%. In the rest of the world such as Japan, Central and Southern Europe, Central Asia and parts of South America the rates are 2-7%.

The condition was first recorded in 1883 when a batch of smallpox vaccine from human sources led to a small outbreak of jaundice. In World War II around 330 000 U.S. army personnel were injected with contaminated yellow fever vaccine of whom around 50 000 developed jaundice. It was later recognised as occasionally following a blood transfusion, the so called 'Homologous Serum Jaundice'. Then in 1965 an antigen was detected in the serum of an Australian Aboriginal; the 'Australia antigen' was subsequently shown to be derived from the viral coat. Since then there has been a breathtaking advance in the knowledge of what we now know is a virus.

4. NATURAL HISTORY

To understand the epidemiology, we need to know the cellular events following infection (4). The virus, present in blood and its products such as semen and saliva settles in the liver after transmission following an incubation period of two to six months. It enters the cell nucleus and undergoes a complex series of changes leading to the appearance in the serum of HBsAg and HBeAg. The virus itself is not particularly aggressive,

cell damage depends upon the processes of the body's immune response. Broadly there are four possible outcomes.

- In two thirds of cases, the cellular response clears the infection after some weeks, most often without clinical illness and even without changes in liver enzymes. HBsAb appear and cure results.
- In maybe 25% there is clinical illness of some weeks followed by recovery both clinical and virological. In a sample of 330 000 U.S. serviceman given contaminated yellow fever serum followed by jaundice in 50 000, 40 years later the carrier rate in the latter was only 0.26%.
- Sometimes the immune response is so vigorous that massive cell damage takes place, even leading to a fatal outcome.
- In about 5-10% of infections the immune response is so muted that, a chronic state of infection persists, defined as more than six months. HBsAg, HBeAg and HBV DNA persist with or without abnormal liver function tests and clinical abnormality.

5. HISTORY OF THE INFECTION

This is most likely to occur in those with a depressed immune system - in neonates, those with leukaemia, AIDS or chronic renal failure. Those with an apparently normal immune system who fail to clear the infection may have normal liver function tests: 'the healthy carrier' state.

6. TRANSMISSION

This is by way of blood, blood products or secretion, saliva or semen. The major routes of infection are:

- At birth. Infants of mothers with high levels of HBeAg have a 70-90% chance of infection which they are unlikely to clear – the so called vertical transmission. The risk falls to 10-40% in infants of infected mothers who are HBeAg negative.
- Childhood infection. Children of infected mothers who escape infection at birth still carry in excess of 50% risk of infection by age 5 but the mode of infection is obscure.
- Sexual transmission. In western societies this is a major source of infection, both heterosexual and homosexual. Risk factors include duration and number of sexual partners, receptive anal intercourse, illicit drug use, sexually transmitted diseases and prostitutes and their clients. Following the appearance of HIV and the public health measures to

control the HIV epidemic, heterosexual activity has become the major mode of transmission.

- Household transmission. The infection is relatively easily transmitted. It carries a risk not only to sexual partners in households with an infected adult but also to children of the house.
- Intravenous drug use. This is an important portal of entry in the western world, and in the U.S. and Western Europe figures of 23% for this mode of transmission are quoted. U.S. experience is that by five years of regular activity Hepatitis B infection is almost universal. The major mode of transmission is by needle sharing.
- Other modes. Workers in the healthcare industry are at particular risk, particularly from those working in residential care such as in the care of the intellectually impaired especially Down syndrome with rates of 3% quoted. Dialysis and dental units also carry a small risk. Use of unsterile medical and tattooing equipment also carry risk. Blood transfusions are now checked by sensitive methods but blood still carries a finite risk.

7. GEOGRAPHIC DISTRIBUTION

For reasons not elucidated, Chinese are less likely to clear the infection than others accounting for the vertical transmission and high prevalence of Hepatitis B in the East. On the other hand in Africa child – child is though to be an important mode.

It is reported that in the U.S. and Western Europe the prevalence of HB is declining. The putative causes are many; public health measures, changing sexual practices, screening of products for transfusion, safer needle practice and vaccination.

8. COURSE AND PROGNOSIS

When infection fails to clear, a low grade inapparent hepatitis persists. Serologically, these patients are characterised by a persistence of HBsAg which seldom spontaneously clears and the presence of HBeAb in most. In the minority the persistence of HBeAg indicates continued viral replication and infectivity. If the hepatitis persists then there is a major risk of increasing hepatocyte loss, fibrosis and cirrhosis; the risk of the latter being about 2% per annum. The risk is higher with increasing age. With cirrhosis comes the risk of hepatocellular carcinoma after several decades of infection. One estimate puts the risk of hepatocellular carcinoma at 6% at

five years after diagnosis of cirrhosis with the risk higher for males and for infections acquired in childhood which explains the higher prevalence of hepatocellular carcinoma in the East than in Europe.

9. TREATMENT (1)

9.1 Curative

Whilst a variety of drugs are now available they fall into two classes, immunomodulation with Interferon α or viral suppression with nucleoside analogues. However, the most that can be achieved is modification of virus replication and its eradication is almost never achieved.

9.2 Preventive Measures

These broadly consist of laboratory produced recombinant vaccines. They are effective, produce good HBsAb levels in more than 95% of recipients and in field trials have proved highly effective with attack rates of 3.2% versus 25.6% for placebo. Universal childhood vaccination is policy in some countries but the cost is a problem in the lesser developed countries. For the immunocompromised such as those on haemodialysis, extra dosage may be required. Ultimately the hope is to entirely eradicate the infection from the world.

Two further aspects require mention. Firstly, there are subtypes of HB virus which vary geographically but may have no clinical significance. Secondly, Hepatitis B infection may be complicated by hepatitis delta (D) infection at any stage. This is a tiny strange RNA virus which can only coexist in the presence of HB virus infection. Its presence may lead to severe and even fatal complicating hepatitis.

Overall the prognosis for the healthy HB chronic carrier suggests little threat to life, but there are unexplained racial differences. Italian children are more likely to clear the infection than Chinese. In the west, although males are more likely to become chronic HB carriers, a healthy adult male acquiring Hepatitis B does well as the experience of U.S. serviceman in World War II attests (5).

References

1. Lai CL, Ratziu V, Yuen MF, Pynard T. Viral Hepatitis B. *Lancet* **362**,2089-2094 (2003).
2. Rizzetto M. Viral Hepatitis. In: Bircher J, Benhamou J-P, McIntyre N, Rizzetto M, Rodes J, eds. *Oxford Textbook of Clinical Hepatology*. 2nd Edn. (OUP, Oxford, 1999), Vol. 1, pp. 827-96.

3. Beringuer M, Wright TL. Viral Hepatitis. In : *Schleisinger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, diagnosis, management.* Feldman M, Friedman LS, Schleisinger MH eds. 7th Edn. (Saunders, Philadelphia, 2002),Vol. 2, pp. 1278-1341.
4. de Franchis R, Meucchi G, Vecchi M et al. The natural history of asymptomatic hepatitis B surface antigen carriers. *Ann. Intern. Med.* **118**,191-4 (1993).
5. Seeff LB, Beebe BW, Hoofnagle JH et al. A serological follow up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. *N.Engl. J. Med.* **316**,965-970 (1987).

Chapter 11c

HEPATITIS C

1. OVERVIEW

This, together with alcoholic liver disease and Hepatitis B, must be one of the most significant liver diseases affecting mankind. It has been estimated that it accounts for 20% of acute hepatitis, 70% of chronic hepatitis and 30% of end-stage liver disease in the United States (1). The ICD 10AM Code is B17. In contradistinction to alcoholic liver disease, its history is a recent one.

Following the development of blood transfusion before World War II and its rapid evolution in the 1940's, it became evident that there were patients developing jaundice some time after blood transfusion. Following upon the discovery of the 'Australia Antigen', subsequently identified as the Hepatitis B virus in the late 1960's and the development of screening methods for blood, there was a major but incomplete fall in the incidence of post transfusion jaundice. 'Non A Non B' virus, hypothesised in 1989, was identified as the Hepatitis C virus which now accounts for 90% of such infections. With a screening assay developed in 1990, enormous strides have been made in our knowledge of the virus and its role in human disease with the development of an enormous literature (2). The Hepatitis C virus belongs to its own genus *Hepacivirus* within the family *Flaviviridae.* As it cannot yet be grown in tissue culture and with no satisfactory animal model, investigating its nature and role is difficult. It seems likely that there are six genotypes, each with subtypes with some debate over classification of the virus which manifests great genetic heterogeneity and readily mutates. Cloned in 1989 it was subsequently patented by the Chiron Corporation creating much debate as to the validity and ethics of the patent (3).

2. PREVALENCE

It has been estimated that about 3% of the world's population is infected but with major variations in distribution of the virus and sub-types. Whilst the post World War II was a low prevalence era, with blood transfusion as the major source of infection, its prevalence has increased due to two factors; intravenous drug use and the widespread use of unsterile medical injection equipment in many parts of the world. In the Australian community it is estimated that about 1-2% have unrecognised Hepatitis C. Blood donors in Australia are rigorously tested and for first time volunteers the rate is $21.5/10^4$, similar to the European experience and considerably lower than that in the US, but these are a select group of volunteers who have already passed strict selection criteria. Prevalence rates in apparently healthy persons range from $1\text{-}2/10^4$ in the UK and Northern Europe,$30/10^4$ in North America, $100\text{-}150/10^4$ in Southern Europe, up to $6500/10^4$ in Equatorial African to even $4{,}000/10^4$ in parts of Egypt (4).

Even in communities not exposed to blood transfusion or injections, Hepatitis C still exists; the persistence of the virus in human society demands it. For example, in isolated aboriginal populations in eastern Taiwan, a Hepatitis C virus prevalence of >20% has been recorded with the mode of transmission still mysterious (5). In like vein, stored sera taken between 1948 and 1954 from military recruits showed a prevalence of 0.2% of hepatitis C antibody. Although it seems that certain types show geographic localization, the last fifty years have seen a major redistribution related to World War II and the Korean War, the growth of the tourism industry and the migratory aspects of the drug culture.

3. TRANSMISSION OF THE VIRUS

The principal routes are:

1. Transfusion of blood and related products
2. Illicit drug injection
3. Prison
4. Tattooing and other body penetration
5. The healthcare setting
6. Sexual transmission
7. Household transmission
8. Ear Piercing

Two essential features relevant to transmission are the almost essential need for body penetration and the high infectivity of the virus - it is about 10

times more infective than HIV per unit of blood (6). In England and Wales, the risk factors (± 1994) were IV drug use (80%) and transfusion (10.8%)(4)

3.1 Transfusion of Blood and Related Products

Before the introduction of adequate testing methods in 1990 the risk of non A - non B Hepatitis was about 1 in 500 units (7), now down to about 1 in 10^5 units. A major contributor to the fall is, in addition to Hepatitis C testing, rigorous donor screening and testing for Hepatitis B and HIV virus, which often coexist with Hepatitis C.

3.2 Illicit Drug Use

This is by far the most significant route of infection in developing and developed countries. There are also suggestions that the 'snorting' of cocaine (8) is significant. It is clear that, in Australia at least, HCV infection was present in drug injectors as early as 1971 and the infection rapidly spread through the drug injecting community. In a comprehensive review of the problem across the world, the seroprevalence of hepatitis C positivity is about 70% in IDU (illicit drug users) with a high of 82.4% in North America (9). The link with Hepatitis B and HIV is evident with prevalences of 62.0% and 19.0% respectively in the global figures. The data indicate that a major predictive factor for HCV positivity is duration of injecting which in turn is linked to the age of the subject. An index was constructed to evaluate the risk of seroconversion - the time to 50% seropositivity in a cohort. In general, the data indicate; - Australia/New Zealand <5->10 years, USA up to 2 years, European Countries with risk reduction programs 3-18 years, and Europe without these programs up to 6 years. Other factors are type of drug: Opiates such as heroin are more harmful than stimulants such as the amphetamines; daily injection is likely to be more dangerous and equipment sharing is more dangerous. However, even in those who deny ever sharing equipment, there is a significant risk of infection, probably related to lifestyle factors and sharing of other facilities.

3.3 Prison

In several studies of prison entrants; seropositivity rates of one third to one half are typical, a not surprising finding given the high prevalence of IDU in prison populations. In prison major risk factors such as needle sharing and a shortage of equipment for sterilization all contribute. Tattooing in prison has also been implicated.

3.4 Tattooing

This has been implicated but there are no data on the size of the risk (8).

3.5 The Health Care Setting

Essentially there are two subsets of this. Firstly in much of the less developed world, injection therapy is widespread and indeed expected by patients; simultaneously facilities, knowledge or sterile equipment are often inadequate. There is overwhelming evidence for a major role for iatrogenic transmission in the developing and undeveloped world, sometimes as a consequence of official policies. A sad example of this is in the Nile Valley in Egypt where there was a concerted effort to counter the schistosomal epidemic with a campaign of parenteral injections with inadequate sterilization during 40 years to the 1980's (10) with the consequence that the HCV positivity rates reached as high as 40%. On average, each person in the developing world receives 1.5 injections annually; for the ill or hospitalised the rates multiply enormously; most injections are unnecessary and in the majority of such countries more than 50% of injections are unsafe. A consequence is 1.3 million deaths annually and up to 4.7 million HCV infection per annum (11, 12). The association of HCV infection with injection therapy has been amply confirmed in Pakistan, Japan, Taiwan and Turkey at least.

A constant concern for healthcare workers is transmission of infection by needle stick injury - a frequent accident in the hospital setting. A literature review suggests a rate of about 6% Hepatitis C infection following needle stick injury from a patient with HCV antibody and positive PCR but transmission has not been reported from a patient without HCV RNA. Transmission from patient to patient has been recorded especially in haemodialysis units (13) and also rarely from surgeon to patient.

3.6 Sexual Transmission

In spite of its obvious major importance to patients and their management this remains controversial. Miriam Alter has argued for its importance, citing evidence that 10% of those with recently acquired Hepatitis C had sexual exposure during the previous six months in which the partner was Hepatitis C antibody positive (8). The United States Centers for Disease Control and Prevention contend that sexual exposure accounts for up to 20% of cases (14). On the other hand Dienstag has argued that sexual transmission is negligible in sex partners and that in those with low risk sexual activity the prevalence in the partner of a Hepatitis C antibody

positive patient was 0-7% (15). No evidence for sexual transmission was found in a large study of asymptomatic hepatitis C blood donors (15, 16) while reports from Canada, France, Italy, UK and Australia all indicate a low risk. Croft's view is that the American attitude may stem from the major disincentives to self reporting intravenous drug use in the US and to inadequate history taking (2).

A study of 94 pregnant women infected by contaminated anti-D immunolglobulin showed that none of the husbands and only three of their 231 children had evidence of Hepatitis C infection (17). A study from Northern Italy reported a minimal contribution of sexual transmission in 221 HCV positive patients and their 514 household contacts (18)

3.7 Household Setting

In countries of low prevalence, as in the West, the evidence for household transmission is very weak, and neither breastfeeding nor mode of delivery is a factor. The risk overall to the baby of mothers with positive HCV RNA is about 10% but in mothers with HCV but without HIV the risk is only about 2% (19).

3.8 Ear Piercing

A significant link with ear piercing has been established in blood donors (8).

4. THE NATURAL HISTORY OF HEPATITIS C INFECTIONS

1. The post-infective period
2. Complications

4.1 The Post-Infective Period

It is now apparent that total clearance of the virus may take place particularly in that minority of patients who become ill with symptoms after infection but it needs emphasizing that the majority of people develop no post-infective symptoms. The rate at which this clearance takes place is unclear but seems to range from 50% (as defined by no HCV - RNA on PCR testing) in those presenting with acute illness to 0% in haemodialysis units; figures of 20% clearance in community studies are typical. If the infection

persists then up to 50% of patients will be HCV RNA positive on PCR third generation testing if they have HCV antibody. Liver function tests, and here the alanine aminotransferase (ALT) is widely used, may be abnormal or not or may fluctuate. In general abnormal liver function tests indicate activity and those with persistently normal liver function tests are most unlikely to progress to cirrhosis (20). About a third of chronic hepatitis C patients have persistently normal ALT with a low risk of progression.

4.2 Complications

- Chronic Active Hepatitis
- Cirrhosis
- Hepatocellular carcinoma

The major complications are chronic active hepatitis, (CAH), cirrhosis and hepatocellular carcinoma (HCC). It is these that largely determine the management and the efforts to investigate and prevent these complications rather than more benign ones.

- Extra Hepatic Complications

These range from cryoglobulinaemia to diabetes mellitus. About half of all patients develop an extra hepatic manifestation at some time; arthralgias are common and most complications have an immunologic basis. The accepted associations are mixed cryoglobulinaemia, glomerulonephritis and porphyria cutanea tarda (21) but there are numerous other, as yet unproven, associations.

5. COURSE AND RISK FACTORS FOR PROGRESSION

Early studies from clinics dealing with chronic liver disease painted a very gloomy picture of the outcome of infection with high rates of relatively rapid progress of the hepatitis to cirrhosis and even HCC. This is a classical example of selection bias; people referred to liver clinics are likely to have significantly abnormal liver function tests and even overt liver disease eg. one large liver clinic study reported 50% cirrhosis at 30 years. It is now recognised that this is not the typical case progression. A more recent study using Markov modelling based upon an extensive literature review has clarified some issues (20). It found that disease progression is generally slow but highly variable and that only a minority develop chronic liver disease. The risk of progression to cirrhosis was estimated at 7% and 20% at 10 and 20 years with risks of mortality of 1% and 4% respectively.

Advanced liver disease was more likely with heavy alcohol intake, coincident HIV or hepatitis B infection or when there was already significant hepatic fibrosis present.

6. POST TRANSFUSION HEPATITIS

A large US study found no excess mortality rate in sufferers of post transfusion HCV infection after 18 years but the liver disease MR was 3% versus 1.5% in controls (22). More than 20% developed cirrhosis over 20 years. Patients who have a blood transfusion are often older and sicker and not representative of the community and so their history of post transfusion hepatitis may not truly indicate what happens in the community.

There are two important studies, one Irish and one German, of pregnant women inadvertently given anti-D immune globulin infected with hepatitis C (23, 24). After 18 years the Irish cohort had 2% cirrhosis; after 20 years the German women had less than 4% cirrhosis. The viral strain was a virulent one and alcohol intake was a factor in five of seven Irish women with cirrhosis.

Determining the course, risk factors and prognosis of Hepatitis C infection is quite difficult for a variety of reasons

1. Only a minority have a symptomatic onset so time of onset is often obscure,
2. Reports from liver clinics show major selection bias; the patients are generally the sicker, more overt cases,
3. Studies of those infected at blood transfusion introduce yet another bias; they are generally sicker and older,
4. The availability of therapy renders intervention-free observation unethical,
5. Case definition by antibody studies includes the false positive tests as well as those where infection has subsequently resolved,
6. Spontaneous resolution may occur and be delayed as long as 45 months,
7. Many patients are from a drug culture and subject to other infections such as Hepatitis B, HIV and other disabilities,
8. In a disease of long duration, adequate follow up is difficult, particularly given the socio-economic status of some patients,
9. Some studies have not explored the role of alcohol use on progression of hepatitis.

Given these factors, one may conclude

- The rate of progression to chronicity is somewhere between 70% and 80% and is lower in those with a symptomatic acute phase,

- Anti-Hepatitis C antibody testing, even using the current third generation tests now available, only indicates that infection has probably taken place as the test is not 100% specific. Detection of current infection requires PCR testing (Polymerase Chain Reaction) to determine current viral replication.
- The proportion of those with chronic Hepatitis C who have normal liver function tests varies within population studies -those attending liver clinics will have abnormal levels but several follow up studies eg. women infected with contaminated anti-D globulin in pregnancy showed that 45% of those with Hepatitis C 18 years later had normal liver function tests and one third of those examined 24 years after an episode of 'Non A, Non B Hepatitis' confirmed as Hepatitis C had normal liver function tests.
- In those with consistently normal liver function tests most studies show only mild to moderate change on liver biopsy.
- About one third of chronic Hepatitis C patients have normal ALT with a low risk of progression
- Long term follow-up studies of patients infected with transfusion related 'non A non B hepatitis' indicate no excess mortality rate over two decades but more than 20% had cirrhosis. However those transfused are likely to be older, sicker and so not representative.
- Studies of patients found to have Hepatitis C at blood donation show that 10 - 20 years later their prevalence of cirrhosis is 2-5% (16). Again blood donors are healthy and likely to be free of HIV, Hepatitis B and possibly alcohol abuse.
- In two cohorts of women infected by contaminated Anti D globulin their course was relatively benign.

Given that the major threats to the health and wellbeing of the patients infected with Hepatitis C are cirrhosis and HCC we need to consider the factors involved

7. RISK FACTORS FOR HEPATITIS C PROGRESSION

Given this we can attempt to evaluate the risk factors for the progression - acute hepatitis - chronic hepatitis - cirrhosis - HCC. The major factors are

- Age
- Gender
- Alcohol intake
- Coinfection with HIV or Hepatitis B

- Obesity
- Viral genotype

7.1 Age

The evidence is that in those with infection beginning beyond age 40 the rate of progression doubles.

7.2 Gender

There is inconclusive evidence that males have a higher rate of progression than females.

7.3 Alcohol intake

There is growing evidence of a major risk from alcohol use in those with Hepatitis C (25) There is also a poorly recognised link, at least in US figures, between alcoholic liver disease/cirrhosis and Hepatitis C infection. There is as yet an unexplained but disproportionately high prevalence of HCV among alcoholic patients with liver disease but with no history of IV drug use. The role of ethnicity and socioeconomic status in this as relevant factors in the US have yet to be determined. One study in those with alcoholic liver disease found equal rates of HCV in IV drug users and in non-users. It seems that there is a synergism between HCV infection and alcohol use with the likely mechanism being alcohol induced enhancement of viral replication, with dire consequences for the liver. There is evidence for a more rapid progression from hepatitis to cirrhosis and also evidence of a more rapid development of the cirrhosis - HCC sequence. A Japanese survey showed a duration of transformation to HCC of 31 ± 9 years in those drinking < 46g of alcohol daily but a reduction to 26 ± 6 years in those drinking more. In those with HCV infection the rate of development of HCC in alcoholic cirrhosis was increased 8.3 times compared with those with those HCV negative and with an HCV positivity rate of 50% to 70% in alcoholics with HCC. Even worse, the disease free survival time in those having HCC resection was halved in those drinking >80g/day compared with the teetotallers. The story gets worse. Even in those patients who remain abstinent whilst on Interferon therapy, the rate of remission was lower in ex drinkers of 70+g/day than in non-drinkers. One study reports a zero rate of HCV clearance in drinkers of up to 70g/day. Indeed abstinence for three years before therapy was necessary before initiation of therapy for a maximum response. From all this comes the recommendation (25) that

alcohol intake be limited to 10g/day with HCV infection. In essence the linkage of HCV infection and alcohol is multifactorial. Even if we accept that alcohol promotes viral replication and progression of liver disease, there will still remain the conundrum of a linkage of HCV infection with alcoholic cirrhosis in patients who deny risk behaviour.

7.4 Coinfection

It is clear that coinfection with HIV on Hepatitis C virus has an adverse effect. For coinfection with Hepatitis B, the effects are complex. Acute Hepatitis B/Hepatitis C coinfection may inhibit the development of chronic Hepatitis B infection whereas Hepatitis B may reduce Hepatitis C severity. It also appears that the concurrence of Hepatitis B and C increases the risk of hepatocellular carcinoma.

With HIV infection, it seems that HIV impairs the immune response to Hepatitis C and increases its infectivity and its progression.

7.5 Obesity

It is likely that obesity hastens the progression of fibrosis within the liver.

7.6 Viral Genotype

These are relevant to the treatment response; genotypes 2 and 3 respond better than 1, 4, 5 and 6.

8. VACCINATION

Currently no vaccines against Hepatitis C are available.

9. TREATMENT OF CHRONIC HEPATITIS C

Enormous effort worldwide has gone into finding and evaluating drugs for the treatment of Hepatitis C. Currently interferon preparations and ribavirin as part of complex treatment regime are the principal drugs used (4).

10. SUMMARY

In spite of its ubiquity throughout the world and an enormous research effort and literature, there are more questions than answers in the course and management of the disease. For the non-hepatologist trying to peer into this arcane world, two messages are relevant; the low infectivity of the disease in the community, and the growing recognition that, in the absence of factors such as alcohol abuse, the better prognosis of the infection than has previously been suggested.

References

1. Hoofnagel J, Hepatitis C: the clinical spectrum of the disease. *Hepatology* **26**(Suppl 1),15S-20S (1997).
2. Crofts N. Descriptive epidemiology of HCV. In: Crofts N, Dore G, Locarnini S eds. *Hepatitis C: An Australian perspective.* (IP Communications, Melbourne, 2001), pp. 220-45.
3. Thompson PR, Locarnini S. Virology and molecular biology of the hepatitis C virus In: Crofts N Dore G, Locarnini S eds. *Hepatitis C: An Australian perspective.* (IP Communications, Melbourne, 2001), pp. 15-31.
4. Booth JCL, O'Grady J, Neuberger J. On behalf of the Royal College of Physicians of London and the British Society of Gastroenterology Clinical Guidelines on the management of Hepatitis C. *Gut* **49**(Suppl 1), i1-i21 (2001).
5. Lin HH, Li YH, Yu JH et al. Ethnic and geographic variations in the prevalence of hepatitis A, B and C among aboriginal villages in Hualien, Taiwan. *Infection* **28**,205-8 (2000).
6. Schreiber GB, Brusch MP, Kleinman SH et al. The risk of transfusion in transmitted viral infections. *N. Engl.J. Med.* **334**,1685-90 (1996).
7. Donahue JG, Munoz A, Ness PM et al. The declining risk of post-transfusion hepatitis C virus infection. *N. Engl. J. Med.* **327**,369-373 (1992).
8. Alter MJ. Epidemiology of Hepatitis C. *Hepatology* **26**,62S-65S (1997).
9. Hocking J, Crofts N, Aitken C, MacDonald M. Epidemiology of the hepatitis C virus among injecting drug users. In: Crofts N, Dore G, Locarnini S eds. *Hepatitis C: an Australian perspective.* (IP Communications, Melbourne, 2001), pp. 260-98.
10. Frank C, Mohammed MK, Strickland GT et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* **355**,887-91 (2000).
11. Kane A, Lloyd J, Zaffran M et al. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world : model-based regional estimates. *Bull. World Health Organ.* **77**,801-7 (1999).
12. Miller MA, Pisani E. The cost of unsafe injections. *Bull. World Health Organ*. **77**,808-11 (1999).
13. MacDonald M, Crofts N, Wodak A, Kaldor J. Transmission of the hepatitis C virus infection. In: Crofts, Dore G, Locanini S eds. *Hepatitis C. An Australian Perspective.* (I P Communications, Melbourne, 2001).
14. Alter MJ. Hepatitis C virus in the United States. *J. Hepatol.***31**(Suppl 1), 8-91 (1999).
15. Dienstag JL. Sexual and perinatal transmission of Hepatitis C. *Hepatology* **26** (Suppl 1), 66S-70S (1997)
16. Alter HJ, Conroy-Cantilena C, Melpolder J et al. Hepatitis C in asymptomatic blood donors. *Hepatology* **6** (Suppl 1),S29-S35 (1997).

17. Meisel H, Reip A, Faltus B et al. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. *Lancet* **345**,1209-11 (1995).
18. Brusaferro,S Barbone F, Andrian P et al. A study on the role of the family and other risk factors in HCV transmission. *Eur. J. Epidemiol.* **15**,125-32 (1999).
19. Dore GJ, Kaldor JM, McCaughan W. Systemic review of role of polyurase chain reaction in defining infectiousness among people with hepatitis C virus. *BMJ* **315**,333-7 (1997).
20. Dore GJ, Freeman AJ, Law M, Kaldor JR. Is severe liver disease a common outcome for people with chronic hepatitis C. *J. Gastroenterol. Hepatol.* **17**,423-430 (2002).
21. Speed B. Extrahepatic manifestation of hepatitis C in: Crofts N, Dore G, Locanini S eds. *Hepatitis C: An Australian Perspective.* I P Communications, Melbourne, 2001), pp.101-116.
22. Seeff LB, Buskell-Bales Z, Wright EC et al. Long-term mortality after transfusion-associated non A / non B hepatitis. *N. Eng. J. Med.* **327**:1906-11 (1992).
23. Kenny-Walsh L. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *N. Engl. J. Med.* **340**,1228-1233 (1999).
24. Weise M, Berr F, Lafrenz M et al. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single source outbreak in Germany – a 20 year multicentre study. *Hepatology* **32**,91-6 (2000).
25. Schiff ER. Hepatitis C and alcohol. *Hepatology* **26** (Suppl 1), 39S-42S (1997).

Chapter 11d

CHRONIC HEPATITIS

Chronic hepatitis is a feature of a multitude of hepatic disorders, from the chronic hepatitis of chronic hepatitis B and C virus affecting millions to the chronic hepatitis of rarities such as Wilson's disease and primary biliary cirrhosis, with an increasing incidence of drug related caused hepatitis.

There is one form which in its frequency, immunological characteristics and clinical significance is worthy of some attention. This is the form variously styled autoimmune hepatitis, previously chronic active hepatitis, juvenile cirrhosis, lupid hepatitis (1, 2). Its incidence may be as high as $1.9/10^5$ with a prevalence of up to $17/10^5$ in Europe. It is apparently found in all races but is uncommon in Japanese apparently because of their different HLA status and contributes about 1 in 5 of patients with chronic liver disease in the U.S. In the half century since the first description it has undergone a number of name changes and definitions. Originally described as a disease of young women with acne, cushingoid features and endocrine changes, it is now regarded as one affecting all ages and about 20% of cases are in males. The condition is characterised by a variety of immunological features which helps separate it from other forms of hepatitis which may resemble it histologically and which enable its subdivision into different types. The cause is unknown but it is clearly not viral but immunological in origin. The disease is not clearly delineated; there are atypical forms with features of other liver disease such as primary sclerosing cholangitis, primary biliary cirrhosis and cryptogenic hepatitis. The bases of treatment are corticosteroids, azathioprine and ultimately transplantation; left untreated the disease is held to be ultimately fatal.

References

1. Czaja AJ. Autoimmune hepatitis. In : Feldman M, Friedman LS, Sleisinger MH, eds. *Sleisinger and Fordtran's Gastrointestinal and liver disease : Pathophysiology, diagnosis, management*. 7th ed. (Saunders, Philadelphia, 2002), Vol. 2 , pp. 1462-1473.

2. Heathcote EJ. Autoimmune hepatitis. In : Yamada T, Alpers DH, Kaplowicz N, Lainel, Owyang C, Powell DW, eds. *Textbook of Gastroenterology*. 4th ed. Lippincott, William and Wilkins, Philadelphia, 2003), Vol. 2, pp. 2366-2373.

Chapter 11e

ALCOHOLIC LIVER DISEASE/CIRRHOSIS

Although cirrhosis is the major end point for excessive alcohol intake and liver damage, there is a sequence leading up to this consisting of fatty liver, alcoholic hepatitis, hepatic fibrosis and cirrhosis in that order (1).

1. FATTY LIVER

This condition is common in most western societies and alcohol excess is a significant cause. It was, until recent decades, seen as the major cause but it is now evident that excess fat in the liver, in affluent societies is often caused by factors other than alcohol.

2. THE NON ALCOHOLIC STEATO-HEPATITIS SYNDROME (NASH)

The ICD 10AM Code is K76.0. To understand the changes in the liver produced by alcohol, it is necessary to be aware of its metabolic consequences. Oral intake of alcohol is followed by its oxidation firstly by alcohol dehydrogenases in the gastric mucosa and then in the liver by another alcohol dehydrogenase and to a lesser extent by cytochrome P450 enzymes. Most of these enzyme systems have genetic variants which may explain some of the variation in susceptibility. The acetaldehyde produced by the above is then oxidized to acetate which is metabolized generally but free fatty acids may be produced in large intake situations with diminished β oxidation of fatty acid and increased synthesis of them and their conversion to triglycerides. Lactate may be produced by reduction of acetate with consequent hyperuricamia and gout. The accumulation of triglycerides

within the liver cells is the major feature of fatty liver. Manifested clinically by a large firm liver with possible moderate elevation of transaminases (AST>ALT), serum alkaline phosphatase and GGTP but no changes in bilirubin or protein levels. The condition may occur within weeks of high intake and resolve equally rapidly on abstinence. If it continues then inflammatory changes may appear and later on fibrotic change – alcoholic hepatitis.

3. ALCOHOLIC HEPATITIS

This, often seen in conjunction with fatty liver, is characterised histologically by liver cell necrosis and neutrophil infiltrate. Clinically there is hepatomegaly, sometimes massive, and often tender, possible splenomegaly, stigmata of chronic liver disease and abnormal liver function tests and biochemical changes even of gross degree and hepatic encephalopathy or bleeding and a fatal outcome in extreme cases. The ICD 10AM Code is K70.1.

There is great variation in susceptibility to alcohol at least in part due to enzyme variation; Chinese and Japanese are poor oxidisers of acetaldehyde and so are intolerant of small amounts of alcohol readily taken by other races. Women have less alcohol dehydrogenase in their gastric mucosa and the rate of alcohol oxidation varies three fold among individuals. As alcohol is water soluble, body size also plays a part. Although not so in all species, nutritional state and intake play no role in the development of alcoholic liver disease in humans. Probably as a result of these factors, only about 10-15% of alcoholics develop cirrhosis.

4. ALCOHOLIC CIRRHOSIS

In the majority of societies this is the most frequent form of cirrhosis with an ICD 10AM Code of K70.3. Its prevalence largely mirrors the per capita consumption of alcohol in the community but its frequency in death certificates follows changes in alcohol consumption by about a decade. It is predominantly a male disorder by a ratio of 2:1 even 10:1 and a significant cause of death; in western Europe the mortality of cirrhosis ($17.8/10^5$), predominantly alcoholic, exceeds that from motor vehicle accidents ($12.3/10^5$). WHO data indicate that the countries with the highest per capita alcohol intake – France, Luxemburg, Spain, Austria and Germany tend to have the highest cirrhosis death rates too but the association is not precise;

Sweden, Denmark, Portugal and Italy tend to have higher mortality rates than their intake predicts (2).

5. RISK FACTORS

The major ones to be considered are:

- Alcohol intake, daily intake, duration, age, total lifetime consumption, type of drink
- Sex
- Heredity
- Smoking
- Coffee intake
- Nutritional factors
- Coexistence with other liver disease, Hepatitis B, Hepatitis C
- Race
- Socio-economic factors

5.1 Alcohol intake

Within the individual the correlation between alcohol intake and liver disease is much closer. Lelbach investigated this and did liver biopsies on 265 alcoholics and claimed to have obtained accurate data on lifetime alcohol consumption (3). He found a remarkably close correlation between alcohol consumption and the likelihood of cirrhosis ($P<0.001$) in the 39 cirrhotics in the group in whom the average 'cirrhogenic' consumption was 180g/day for 25 years. The data from this relatively small study indicate that the alcohol intake, measured as grams/kg body weight /day x years, closely mirrors the percentage probability of cirrhosis in males. In a case control study from Canada (4) the RR for biopsy verified cirrhosis in men consuming 40-59 grams of alcohol /day was 1.83 (.76-4.42) compared to those taking <40g/day and for men consuming >80g/day it was 100 (31.6-315.9) (4).

5.2 Sex

Women were more vulnerable; for those consuming 20-59g/day the RR was 2.53 (1.0-6.4) compared with those taking <20g/day and rose to 12.21 (3.54-42.14) for those taking more than 60g/day. The mean daily alcohol consumption in female cirrhotics was 29.7g/day; in males 98.2g/day. The patients were from six hospitals in Toronto seen over a year and the controls

were from a variety of local industries and they had blood liver enzyme levels estimated and a detailed history taken. Comparisons were done with controls regardless of enzyme levels or history of liver disease and also with these excluded for comparison. In general duration of drinking was irrelevant, the significant risk factors were age, daily consumption ($P<0.0001$ in males and $P<0.015$ in females) and total lifetime consumption ($P<0.0001$ in M, $P<0.01$ in F in either sex). Further evidence of the sensitivity of females to alcohol was in the estimated lifetime consumption of absolute alcohol, 163kg (range 0-2317kg) compared with males 499kg (range 0-2581kg). It is of interest that the male consumption ranged up to 2581kg or 2 ½ tonnes of absolute alcohol! The figures are consonant with those of Lelbach above. On his data a 75kg male drinking 98.2g alcohol daily, the mean of the Toronto male cirrhotics, for 30 years would have a 98.2/75x30=40% probability of cirrhosis. The data are also consonant with the only data of substance on 'cirrogenic' level of alcohol use. Pequignot and his group have concluded that 80-160g daily is potentially cirrhogenic with a high risk at level of 160g daily or above. They have also found a risk of cirrhosis in women begins at levels as low as 20g/day (5, 6).

5.3 Heredity

The only study originates in an enormous database, those 15924 twin pairs of white males born between 1917 and 1927 who served in the US Armed Forces. An extremely complex analysis was done, given major genetic variations in drug handling (7). Concordance rates for alcoholism, alcoholic psychosis and alcoholic cirrhosis were greater in monogygotic than in dizgotic twin pairs providing "evidence in favour of genetic pre-disposition to organ specific complications of alcoholism". Most of the observed twin concordance of alcoholic cirrhosis was not a direct consequence of concordance for alcoholism, suggesting that apart from the actual intake of alcohol there is a genetic factor in the pre-disposition to developing cirrhosis.

5.4 Coffee

A strange finding of a protective effect of coffee drinking was found in a study of 128934 adults enrolled in a Kaiser Permanente Medical Care Program in California. The adjusted RR for hospitalization (0.2) and for death (0.7) from alcoholic cirrhosis for drinkers of ≥ 4 cups of coffee per day showed a highly significant risk gradient inversely proportional to coffee intake. Tea was ineffective. No effect was seen on hospitalization for non-alcoholic cirrhosis (8). The beneficial factor is obscure; while most attention

has focused on the caffeine content of coffee, there are 600 chemicals in a roast coffee bean. The finding appears real being present in many subsets studied.

5.5 Cigarette Smoking

The Kaiser Permanente study also looked at smoking with important results. The adjusted RR for hospitalization (3.0) or death (3.3) for alcoholic cirrhosis in smokers was significant ($P<0.05$) with no significant elevation for non-alcoholic cirrhosis (8). However, smoking is strongly associated with drinking and untangling the association is a formidable task yet to be undertaken.

5.6 Nutritional Status

In the mid twentieth century much attention was given to nutritional factors in liver disease but it is now generally agreed that, apart from gross examples of malnutrition as seen in the East, nutritional status has little relevance. However it is not clear that the subject has been adequately studied in recent decades.

5.7 Socio-economic Status

Disentangling the complex interaction of heredity, childhood and adult environment, education, income and race, and the problems of cause and effect make this difficult. The Kaiser Permanente study found race was not a factor but by definition enrollees could afford to insure themselves. Similarly, the RR of alcoholic cirrhosis was only 0.2 (0.1-0.5) in white college graduates. Similarly currently being married was protective, RR 0.4 (table 2 of this paper almost certainly incorporates a typographical reversal of figures).

6. CO-EXISTENCE OF OTHER LIVER DISEASES

There is strong evidence that the co-existence of alcohol use/abuse and Hepatitis B and C hastens the onset of cirrhosis even in small amounts (See chapters on Hepatitis B and C).

7. SUMMARY

Alcoholic cirrhosis is an important cause of morbidity and mortality in the western world. While it is axiomatic that its cause is excessive use of alcohol, through mechanisms not yet fully elucidated, its course and development are subject to modifications by a wide variety of agents. Given that the major determinants are the daily intake and total life-time intake, with females more sensitive, it is clear that there are genetic factors at work, not only in the proclivity to abuse alcohol but in the sensitivity of the liver to assault by alcohol.

For obscure reasons coffee clearly is protective and smoking is probably a positive risk factor. While prohibition has its diminishing band of enthusiasts on a population wide basis, exortations to avoid alcohol excess are probably fruitless. The consumption of alcohol in the community is log-normally distributed and to reduce the frequency of heavy use it is necessary to move the distribution curve to the left which can only be done by reducing the standard deviation of the mean alcohol intake in the community by encouraging those who drink little to drink more or by reducing the total community consumption of which price manipulation is one important factor.

References

1. Sherlock S, Dooley J. Alcohol and the liver. In : Sherlock S, Dooley J. *Diseases of the liver and biliary system.* 10th ed. (Blackwell Science, Oxford, 1997).
2. Salaspuro M. Epidemiological aspects of alcoholic liver disease, ethanol metabolism and pathogenesis of alcoholic liver injury. In : Bucher J, Benhawou JP, McIntyre N, Rizeto M, Rodes M eds. *Oxford Textbook of Hepatology* 2nd ed. (OUP,Oxford, 1999), pp.1157-78.
3. Lelbach WK. Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. *Ann. N. Y. Acad. Sci.* **252**,85-105 (1975).
4. Coates RA, Halliday ML, Rankin JG, Feinman SV, Fisher MM. Risk of fatty infiltration or cirrhosis of the liver in relation to ethanol consumption : a case control study. *Clin. Invest .Med.* **9**,26-32 (1986).
5. Pequignot G, Tuyns AL, Berta JL. Ascitic cirrhosis in relation to alcohol consumption. *Int. J. Epidemiol.* **7**(2),113-20 (1978).
6. Tuyns AJ, Pequignot G. Greater risk of ascitic cirrhosis in females in relation to alcohol consumption. *Int. J. Epidemiol.* **13**,53-7 (1984).
7. Hrubec Z, Omenn GS. Evidence of genetic predisposition to alcoholic cirrhosis and psychosis : twin concordance for alcoholism and its end points by zygosity among male veterans. *Alcohol Clin. Exp. Res.* **5**,207-215 (1981).
8. Klatsky KL, Armstrong MA. Alcohol, smoking, coffee and cirrhosis. *Am. J. Epidemiol.* **136**,1248-57 (1992).

Chapter 11f

NON ALCOHOLIC STEATHOHEPATITIS (NASH)

1. DEFINITION

NASH is a condition characterised by a necroinflammatory component in hepatic macrovesicular steatosis. It is also known as, and is part of a spectrum variously called, non alcoholic fatty liver disease (NAFLD), pseudo alcoholic liver disease, fatty liver hepatitis steatonecrosis and diabetic hepatitis. Histologically it resembles alcoholic hepatitis with inflammatory changes together with a widespread accumulation of large fat vesicles within liver cells. By definition, alcohol abuse is excluded as a cause. Although it has been reported to be found in 6% of autopsies, it was only brought into clinical prominence by a major clinical report in 1980 (1). The ICD 10CM code is K76.0.

2. CLINICAL SETTING

The clinical situations in which it occurs are fairly well delineated:

2.1 Metabolic

- obesityand type 2 diabetes mellitus account for the vast majority of cases. They are associated with raised insulin levels, hyperlipidaemia and probably account for at least 70% of cases. The metabolic syndrome (2) may be associated with NASH

- jejunoileal bypass surgery
- prolonged total parenteral nutrition
- prolonged high dose corticosteroids
- severe malnutrition e.g. severe inflammatory bowel disease.

2.2 Drugs

Many drugs have the potential to produce NASH including amiodarone, perhexiline maleate, tetracycline, calcium channel blockers and tamoxifen.

3. PREVALENCE AND EPIDEMIOLOGY

No good data are available. It seems likely that NAFLD is one of the most common liver diseases in the world, affecting all ages with a prevalence as high as 76% in obese subjects. As the condition is generally silent with possible minor elevation of transaminases with or without an elevated SAP and generally hepatomegaly, exact figures are unlikely to be forthcoming. In the obese its prevalence may be 1-4% at liver biopsy, but by definition this is a select group but it has been estimated to affect 10-24% of the population in selected countries (3). However, the combination of obesity and diabetes is frequent. With obesity so frequent in middle aged females, so it predominates in females in the sixth decade.

4. NATURAL HISTORY

This, yet to be outlined, will be a difficult task. Its diagnosis demands a liver biopsy or, as a minimum, exclusion of other disorders, yet most cases are silent making liver biopsy available only in selected patients. Until liver imaging techniques achieve higher reliability or a non-invasive test for the hepatitis is described, our knowledge will be clouded by descriptions limited to patients selected either for hepatomegaly or for abnormal liver function tests which we know are not an essential feature of the condition. As NAFLD, given a broader definition, it ranges from fatty liver with at least 5-10% of liver weight being fat to combined fat and inflammatory changes to these plus fibrosis and even cirrhosis and in a minority of cases hepatocellular carcinoma.

A favoured theory current is the two hit hypothesis (4). The first “hit” leads to accumulation of fat and free fatty acids within the liver cells. This leaves the liver cells vulnerable to the “second hit” which leads to liver cell

death and inflammatory changes. Whatever the precise mechanisms involved, it is clear that a raised plasm insulin and insulin resistance have an intrinsic role in the pathogenesis of the changes, probably in association with an increased plasma free fatty acid level. A recent extensive review canvases these issues (5).

The original description (1) suggested that the condition may lead to cirrhosis.

Since then there have been two relatively large series reaching contrary conclusions. A report of 42 patients followed for a median of 4.2 years indicated that, apart from two with a lipodystrophy, all were obese. Most were women and about half were hyperglycaemic. Their course was, in general, benign. One patient progressed from fibrosis to cirrhosis and ultimately to hepatocellular carcinoma but most showed no progression. The hepatic changes did not correlate with obesity, glycaemia or lipidaemia (6). On the other hand in a report of 33 patients, the majority were men, non-obese, and with normal lipid and glucose levels. All had biopsy proof. Severe progressive disease was found is 13 of the 33 with fibrosis in 13 and cirrhosis in 5. Alternative diagnoses, in particular viral hepatitis and alcohol abuse, were excluded (7).

5. TREATMENT

There are no adequate studies of any intervention of benefit, but clearly weight loss, at least in the obese is mandatory, although rapid weight loss may produce major liver damage.

6. SUMMARY

Only being recognised clinically within the last few decades, with the growing concern about obesity in the developing world, it is clear that major efforts will, and are, being put into delivering the pathogenesis, significance and outcome of this strange disorder.

References

1. Ludwig J, Viggiano TR, McGill DB, Ott BJ. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin. Proc.* **55**,434-8 (1980).
2. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C for National Heart, Lung and Blood Institute/American Heart Association Conference. Definition of Metabolic Syndrome. *Circulation* **109**,433-9 (2004).
4. Alba LM, Lindor K. Non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther.* **17**,977-86 (2003).

4. James OFW, Day C. Non-alcoholic steatohepatitis: another disease of affluence. *Lancet* **353**,1634-6 (1999).
5. Festi D, Colecchia A, Sacco T, Bondi M, Roda E, Marchesini G. Hepatic steatosis in obese patients : clinic aspects and prognostic significance. *Obesity Reviews* **5**,27-42 (2004).
6. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis : a follow-upstudy of forty-two patients for up to 21 years. *Hepatology* **11**,74-80 (1990).
7. Bacon BR, Fahahvash MJ, Janney CG, Neuschwander-Tetri BA. Non-alcoholic steatohepatitis : an expanded clinical entity. G*astroenterology* **107**,1103-9 (1994).

Chapter 11g

HAEMOCHROMATOSIS

(Hereditary Haemochromatosis, Genetic Haemochromatosis)

1. DEFINITION

Haemochromatosis is a disorder now recognised as having a genetic basis with the genetic abnormality recently identified (1). It is characterised by excessive iron deposition in the tissues essentially the liver, genetically determined by recessive genes on the short arm of chromosome 6. The ICD 10AM Code is E83.1. A consensus meeting recently has redefined hereditary haemochromatosis (HCC) in the light of new knowledge as "an inherited disorder resulting from an inherited error of metabolism which leads to progressive iron loading of the parenchymal cells of the liver, pancreas and heart. In its fully developed stage, organ structure and function are impaired" (2). The definition expressly excludes mention of tissue damage for it is now recognised that in many people expression of the gene is minimal. The condition, first described by Trosier in 1865, and characterised by cirrhosis of the liver, diabetes mellitus and pigmentation, is rare. However, the disease is now recognised as being reasonably frequent but with much less florid manifestations. The clinical picture and its hereditary basis were not clarified until 1935 when Sheldon published a study of more than 300 patients.

Until the demonstration of a defective gene (HFE) on chromosome 6 (1) in 1996 a vigorous debate had taken place in recent decades about the classification and pathogenesis of various iron overload syndromes which may present a similar clinical picture. Briefly these are:

- Secondary Iron Overload which occurs in disorders of erythropoiesis.
- Iatrogenic iron overload from prolonged oral iron therapy.

- African iron overload ('Bantu cirrhosis') due to the high iron content of beer brewed in iron containers.
- Neonatal iron overload.

2. PATHOGENESIS

The basic mechanism for haemochromatosis (HHC) is an excessive absorption of dietary iron leading to tissue deposition or iron, particularly in the liver, pancreas, pituitary and heart with subsequent tissue damage, fibrosis and functional impairment; later in the disease iron deposition occurs in the reticuloendothelial system.

To understand the cause and course of HHC it is necessary to review the way the body handles iron, in particular its ability to absorb and excrete it. Normally, a western diet contains about 10-20mgs of iron daily of which about 10% is absorbed and utilized predominantly in haemoglobin, myoglobin and various enzymes (3g) and 0.5g as storage iron. Dietary iron is absorbed to compensate for iron loss by epithelial exfoliation and GI loss to account for 1mg/day in males and 2mg/day in menstruating females. In classical HHC the body iron load is commonly 20-60g against the normal 5g. In HHC the absorption of iron is increased. It is then transported from the enterocyte by attachment to transferrin which, instead of the normal transport to the reticuloendothelial system in the marrow, deposits undue amounts of iron in the parenchymal cells of the liver with a complex chain of events leading to tissue damage, fibrosis and even cirrhosis. It is thought that a similar event takes place in other organs, especially in the pancreas, anterior pituitary, thyroid, parathyroid, heart, testes and joints with the potential for impairment or even failure of these organs.

3. THE GENETIC DEFECT

This has been localized to the short arm of chromosome 6 and the common form is described as C282Y i.e: there is at the critical site the substitution of cysteine by tyrosine but other anomalies such as H63D mutations where the substitution of histidine by aspartic acid (H63D) have been described to account for about 15% of clinic disease. About 10% of cases of HHC remain unexplained by these two. The HHC gene is recessive but the heterozygote is remarkably common in Caucasians at about 10% which is one of the highest prevalences of gene abnormality. This means that the homozygote frequency is about 0.5% in northern Europeans. Possession of the heterozygote gene causes little disability and to account for

its frequency it has been suggested that possession of the heterozygote carries a small advantage by protecting against iron deficiency. It is also suggested that the original mutation arose in a Celtic or Viking population 2000 years ago in Brittany.

4. PREVALENCE AND RISK FACTORS

Although the florid disease is quite unusual, HHC is being recognised increasingly because of the interest engendered by genetic studies and by recognition of its role in presentations such as polyarthritis and diabetes which affect two thirds of those with the developed disease. The clinical syndrome of HHC most frequently presents in males between 40 and 50 years of age with male predominance of 10-1.

5. ALCOHOL

There is evidence of a link with alcohol abuse which is frequent in HHC patients; alcohol abuse accelerates iron absorption and progression of the disease and there is also some evidence of pancreatic insufficiency – a not uncommon accompaniment of chronic alcoholism – increases iron absorption. Until identification of the genetic abnormality it was felt that clear linkage of the gene to HHC would permit early identification iof susceptibility with all homozygotes eventually developing clinical disease. A recent large exhaustive study of 41 038 people attending a Health Appraisal Clinic in California has clarified the issue (3). The findings were remarkable. No symptoms were more frequent in homozygotes (152 with C282Y/C282Y and 616 compound heterozygotes C282Y/H63D) than in controls. After controlling for age and sex, homozygotes were twice as likely as controls to report a history of liver problems or have raised AST than controls but only 19% as likely to report skin darkening. Otherwise homozygotes were indistinguishable from controls in terms of symptoms and laboratory findings apart from abnormal serum ferritin and transferring saturation findings. Virtually all the homozygotes were of white or mixed/white ancestry. Calculation of the Hardy-Weinberg equilibrium data for those claiming ‘white only’ ancestry showed a prevalence of the C282Y gene of 0.06 thus predicting a homozygosity prevalence of 3.872×10^{-3} against an observed 4.6×10^{-3} for males and 4.4×10^{-3} indicating no selective homozygote loss from the population.

6. THE NATURAL HISTORY OF THE DISEASE

The natural history is yet to be written. Genetic studies indicate that many homozygotes are in normal health and there is a report of 492 French centenarians of whom two were homozygotes, the same as controls. It is becoming increasingly evident that the full phenotopic expression of the homozygote is quite unusual for reasons not yet determined and that overall homozygotes have a normal life expectancy.

7. THE ROLE OF SCREENING

There is an emerging consensus that, in view of the growing evidence of the low rate of penetrance and consequently of impairment of health and longevity population screening is not indicated (5).

References

1. Feder JN, Gnirke A, Thomas W et al. A novel MHC class 1 – like gene is mutated in patients with hereditary haemochromatosis. *Nat. Genet* . **13**,399-411 (1996).
2. Adams P, Brissot P, Powell L. EASL International Conference on haemochromatosis – part II. Expert document. *J. Hepatol.* **33**,487-96 (2000).
3. Beutler E, Feletti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845 G→A (C282Y) HFE hereditary haemochromatosis in the USA. *Lancet* **359**,211-8 (2002).
4. Coppin H, Bensaid M, Fruchon S, Borot N, Blanche W, Roth MP. Longevity and carrying the C282Y mutation for haemochromatosis on the HFE gene : Case control study of 492 French centenarians. *BMJ* **327**,132-3 (2003).
5. Pietrangelo A. Hereditary haemochromatosis – a new look at an old disease. *N. Engl. J.Med* . **350**,2383-97 (2004).

Chapter 11h

HEPATOCELLULAR CARCINOMA

1. DEFINITION

Primary hepatocellular carcinoma (HCC) is a malignant tumour of liver cells associated most frequently with chronic viral hepatitis or cirrhosis. Less frequent causes include environmental toxins and hereditary haemochromatosis. Its ICD 10AM Code is C22.0. The prognosis is in general poor due to late diagnosis and the advanced state of liver disease usually found in these patients. Worldwide HCC results in between 250 000 and one million deaths annually with a wide geographic variation in the distribution of the disease consistent with its known causes. The development and dissemination of a vaccine for Hepatitis B should result in a fall in HCC in endemic areas.

2. NATURAL HISTORY

HCC develops as small nodules in the liver that are asymptomatic until late when there is invasion of surrounding structures. There is no convincing evidence that the aetiology of the tumour determines aggressiveness. The key factors influencing survival untreated are the severity of the underlying liver disease and tumour size. Untreated 50-90% of Child-Pugh A cirrhosis will survive one year compared with only 20% with Child-Pugh C. Survival with tumours smaller than 5cm is up to 100% at one year and approximately 20% at three years without treatment (1).

3. EFFECTS OF INTERVENTION

Detection of earlier lesions by ultrasound or measurement of tumour markers has not been shown to improve long term survival. The only proven potentially curative treatment for HCC is surgical resection or liver transplantation but chemoembolisation can produce tumour necrosis and be effective for pain or bleeding. Hormonal therapy with Tamoxifen has shown no survival benefit in controlled trials.

4. ASSOCIATIONS

Cirrhosis is present in the vast majority of patients with HCC (2). Non cirrhotic HCC occurs occasionally in viral liver disease, particularly with HBV and occurs rarely in HCV infection and haemochromatosis. Familial clustering of HCC, though common, is due to vertical transmission of HBV and not genetic predisposition.

5. SECULAR CHANGES

The incidence of HCChas been rising in the last three decades and more recently in the west including the US, France and the UK (3). The proportion due to HBV is falling in these areas while that due to HCV is rising and 3-6% of patients with HCV cirrhosis develop HCC annually (4).

6. AGE

As HCC most frequently develops in the cirrhotic liver, most patients with HCC are older with a mean age at presentation of between 50 and 60 years.

7. GENDER

Males are far more likely to develop HBV related HCC than females particularly in high incidence regions due to variations in hepatitis carrier rates, exposure to environmental toxins and the effect of androgens. The difference is less for HCV related tumours.

8. INCIDENCE AND GEOGRAPHIC FACTORS

Globally the incidence of HCC varies markedly between high, intermediate and low incidence areas consistent with the distribution of the major risk factors, particularly Hepatitis B.

- High Rates (more than 20 per 10^5 per year)
- Over 40% of all cases of HCC occur in the People's Republic of China with an annual incidence of 137,000 cases. Other high incidence areas include sub-Saharan Africa, Hong Kong, Japan and Taiwan.
- Intermediate Rates (5-20 per 10^5 per year)
- These occur in Singapore, Malays and Indians, Thailand, Indonesia, Jamaica, Haiti, New Zealand Maoris and Canadian Inuit.
- Low Rates (<5 per 10^5 per year)

These areas are New Zealand, Australian, Canadian and UK whites, whites and blacks in America, Sweden, Denmark, Germany, Israel, India and Pakistan.

The differences in distribution of HCC are largely due to regional differences in exposure to hepatitis viruses and environmental toxins. The incidence in the United States has increased during the past two decades, partly due to the large pool of people with long standing chronic Hepatitis C from blood transfusions before the introduction of Hepatitis C testing and from IV drug use. The interval between acquisition of HCV and the development of cirrhosis and its complication is thought to be about 30 years (5).

9. GENETIC FACTORS

There is no evidence for a genetic predisposition to HCC.

10. CAUSES OF HCC

It is unclear whether cirrhosis per se is biologically important in the tumorigenic pathway, or if tumour development and fibrogenesis take place concurrently. The causes of cirrhosis include the Hepatitis B carrier state, environmental toxins, chronic Hepatitis C virus (HCV) infection, hereditary haemochromatosis and cirrhosis from almost any cause. The risk of HCC development in cirrhosis due to auto immune hepatitis, primary sclerosing cholangitis in either sex and alcoholic and primary biliary cirrhosis in women is generally low. Non cirrhotic HCCs do occur in viral hepatitis but the absolute risk is low.

10.1 HBV

HBV infection with cirrhosis carries a high risk of development of HCC of the order of 1.5% annually. Infection early in life and development of the HBV carrier state are strongly associated with HCC. HBV can be involved in the pathogenesis of HCC even in those who are HBsAg negative as these patients may still have evidence of infection using molecular techniques (6). The risk of HCC is also higher in patients who are HBeAg positive compared to those who are HBsAg positive but HBeAg negative (324 v $39/10^5$ person years). Cirrhosis increases the risk of HCC as may other hepatotrophic stimuli, such as alcohol and cigarettes that act synergistically in the pathogenesis of HCC.

10.2 HCV

HCV cirrhosis and HCV carriers have a higher risk of HCC of about 3-5% p.a. Genotype 1b may be a bigger risk factor than genotype 2 and 3 having been associated with more severe liver disease, however duration of infection appears to be more important that genotype.

10.3 HCV and Alcohol

Alcohol acts synergistically with HCV to increase the risk of HCC. Moreover the prevalence of anti-HCV has shown to be higher in patients with alcoholic cirrhosis and HCC (76%) than in patients with alcoholic cirrhosis alone (38.7%) (7).

10.4 HBV and HCV

The combination of HCV and HBV infection appears to augment the risk of developing HCC (8).

10.5 Cigarette Smoking

Its role in the development of HCC is controversial.

10.6 Haemochromatosis

HCC is virtually limited to those patients with hereditary haemochromatosis who develop cirrhosis. The risk is high and about 7-9%

p.a. The increased risk (1-3% p.a.) seen in less severe diseases may be due to the amount of mobilizable iron and delay in initial treatment.

10.7 Other causes of cirrhosis

The risk of HCC among patients with cirrhosis from PBC, Wilson's disease and auto immune causes seems to be slightly increased but difficult to quantify.

10.8 Aflatoxin and Betel Nut

Aflatoxin, a mycotoxin that commonly contaminates corn, soybeans and peanuts and microcystin blue-green algal toxin that contaminates drinking water have both been associated with an increased risk of HCC. Betel nut chewers, frequent in Asia, may also have an increased risk of cirrhosis and HCC.

10.9 Alcohol

The relationship between alcohol and HCC is unclear and may be related to the development of cirrhosis rather than alcohol being a direct carcinogen. It is estimated HCCs develop at about 1-4% p.a., similar to the rate in HCV and HBV cirrhosis.

10.10 The Oral Contraceptive Pill

The risk of HCC from prolonged use of the OCP is small if it exists at all.

References

1. Barbara L, Benzi G, Galani S. Natural history of small untreated hepatocellular carcinoma in cirrhosis; a multivariate analysis of prognostic factors of tumour growth rate and patient survival. *Hepatology* **16**,132-7 (1992).
2. Giarelli L, Melato M, Zanconati F et al. Primary liver cancer in non-cirrhotic liver. Epidemiological study based on autopsies performed in Trieste, Italy and Kurume, Japan. *J .Gastroenterol .Hepatol.* **6**,278-82 (1991).
3. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N.Engl. J. Med.* **340**,745-50 (1999).
4. Okuda K, Takayasu K. Primary malignant tumours of the liver : in Okuda K (ed) Hepatobiliary diseases. (Blackwell Science, Oxford, 2001).
5. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma : A population-based study. *Gastroenterology* **127**,1372-80 (2004).
6. Liang TJ, Jeffers LJ, Reddy R et al. Viral pathogenesis of hepatocellular carcinoma in the United States. *Hepatology* **18**,1326 (1993).

7. Bruix J, Barrera JM, Calvet X et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* **2**(8670), 1004-6 (1989)
8. Colombo M, Kuo G, Choo QL, Donato MF, Del Ninno E, Tommasini MA, Dioguardi N, Houghton M. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* **2** (8670):1006-6 (1989).

Chapter 11i

ACUTE AND CHRONIC CHOLECYSTITIS

1. DEFINITION

Cholecystitis – inflammation of the gall is one of the most frequent disorders of the alimentary tract. The ICD 10AM Code is K81. Although classically it has been subdivided into the acute and chronic varieties, it is likely that they are both part of a spectrum which is most often caused by gall stones. It is necessary, however, to emphasise that the majority of gall stones remain asymptomatic and cholecystitis develops in 1-3% of persons with them (1).

Classically acute cholecystitis manifests as an acute right hypochondrial pain lasting from minutes to hours, often beginning at night and often in young women. The pain, in contradistinction to that of biliary colic, lasts longer than 6 hours but in three quarters of episodes of acute cholecystitis, the patient gives a prior history of biliary colic. The acute pain, often with vomiting, radiates to the back and in one third of cases, the gall bladder becomes palpable as it distends. If the acute episode fails to resolve then infection is likely to supervene, generally with E.coli, Klebsiella or S.faecalis, producing an acute inflammatory process in the gall bladder with pain, nausea, vomiting, fever; later a mass in the right hypochondrium may appear. It is estimated that in 90% of cases obstruction of the neck of the gall bladder by stone or sludge initiates the process. The gall bladder then becomes distended with supersaturated bile leading to inflammation in the wall with prostaglandin liberation. This finding has led to the use of NSAIDs in acute cholecystitis; given early they are beneficial in reducing inflammation. In about half of the patients the stone drops back into the gall bladder, relieving the obstruction but in about 20% of patients, resolution

fails to occur and cholecystectomy is necessary. If left untreated, about 10% of cases go on to a complication such as perforation and even peritonitis.

A variant of acute cholecystitis is acalculous cholecystitis where acute and chronic cholecystitis may occur in the absence of a stone. It is seen particularly after surgery, trauma and burns and in elderly males. Mucocoele of the gall bladder occurs when an obstructed gall bladder does not become infected and the bile is replaced by mucus. Empyema of the gall bladder occurs when the gall bladder appears to be filled with pus but in half such cases the fluid is sterile.

2. DESCRIPTIVE EPIDEMIOLOGY

Remarkable for such a common condition, the literature is largely silent on solid data concerning the epidemiology. The topic cries out for epidemiological studies.

3. INCIDENCE AND PREVALENCE

Apart from simple statements largely applying to western societies, the literature mainly concerns the surgical aspects such as the management, timing and the nature of surgical intervention and investigation.

References

1. Indar AA, Beckingham IJ. Acute cholecystitis. *BMJ* **325** (7365):639-43 (2002).

Chapter 11j

CHOLELITHIASIS

1. DEFINITION AND OVERVIEW

Cholelithiasis is the presence of solid concretions within the gall-bladder or, less often, within the biliary tree. Stones in the gall-bladder are found in 10-20% of the population throughout the world but with considerable variation. Likewise, cholecystectomy for stone is a common operation with 750,000 done in the USA annually. The ICD 10AM Code for cholelithiasis is K80. Whilst gall stones are rare in childhood, they increase in frequency thereafter and the several varieties show major geographic variations. X-ray diffraction studies show that the majority of stones are mixtures of cholesterol and derivatives, bile salts, bile pigments and minerals. Pure cholesterol stones do not occur; and it has been claimed that one in five stones are entirely mineral in composition, justifying the term "rocks" sometimes used in surgery (1).

A current classification is:- (Table 4)

cholesterol stone

black pigment stone

brown pigment stone (2)

The causes of gall stones are far from clear (3). It is known that those with cholesterol gall stones have supersaturated bile but the actual mechanisms producing the supersaturation and that provoking cholesterol precipitation are not clear. Cholesterol is water insoluble; its solubility in bile depends upon adequate amounts of bile acid and phospholipid. So in those with cholesterol stone, there is either:

excess liver secretion of cholesterol or,

impaired biliary secretion of bile acid and phospholipid or,

impaired gall bladder motility.

However, there are other factors at work to promote or inhibit cholesterol deposition with protein playing an important role - gall bladder sludge, mucoprotein with entrapped cholesterol microcrystals is probably an important precursor in stone formation.

Cholesterol synthesis is determined by the enzyme HMG Co A reductase (hydroxymethyl glutaryl coenzyme A reductase) whose activity is governed by plasma insulin levels. This explains the association of gall stones with obesity in which insulin levels are increased. There is also evidence that some stone bearers have poorly contracting gall bladders. In western societies, cholesterol stones predominate but in spite of considerable physiological and epidemiological research their ultimate cause remains obscure (3).

Pure pigment stones are frequent in the West, increase in prevalence with age and are associated with biliary disease, cirrhosis and haemolytic processes. On the other hand bile pigment - calcium stones are common in the East and seem to be associated with anaerobic bacterial contamination of the biliary tree. It seems likely that β glucuronidase from these organisms hydrolyses the bilirubin glucuronide complex liberating bilirubin which precipitates as calcium bilirubinate. In less developed countries in the East, parasite residues such as eggs or fragments of Ascaris lumbricoides have been identified in calcium - pigment stones.

Table 4. Gall Stone Characteristics

	Cholesterol	**Black Pigment**	**Brown Pigment**
Constitution	cholesterol, usually single	bilirubin polymer multiple, facetted	calcium bilirubinate + calcium palmitate
Site	gall bladder and ducts	gall bladder and ducts	ducts
Aetiology	supersaturated bile + ?	excess bilirubin production and cirrhosis	biliary infection, stasis
Geography	affluent west	affluent west	Asia
Frequency	usual in west (75%)	20%	usual in the East

2. DESCRIPTIVE EPIDEMIOLOGY

The development of ultrasound has facilitated research but the combined figure for ultrasound detected stone + prior cholecystectomy, almost always done for stone, provides better prevalence figures than figures from cholecystography, often done for symptoms in the past.

2.1 Age

The prevalence rises with age. In eight European studies the prevalence of gall stone disease (ultrasound detected plus cholecystectomy) reached about 30% in females aged 60-69 years from a level of about 5% in the 20-29 age group. In males the figure reached ± 10% at age 60-69. They are especially common in Scandinavia and a study from Bergen, Norway showed remarkably high prevalence rates - over 40% in females 60-69 years and slightly less in males (4).

2.2 Gender

Gall stones are more frequent in females but the surgical aphorism that "fat, fertile, females over forty" characterizes gall stone patients is fallacious. In general, the M:F ratio is about 1:2 throughout the world.

2.3 Ethnicity

There are remarkable variations in prevalence between ethnic groups and even within them. Two outstanding examples are the Pima Indians of southern western United States (5) and the Amerindians of Chile (3), both of whom have very high rates. The autopsy prevalence (not age adjusted) in Chile is reported as 42% in females and 16.7% in males compared with figures in the low 20's for females in Sweden, Czechoslovakia and Scotland and 14% for the US and Australasia down to 4.2% in Thailand (6).

2.4 Secular Trends

Few data on secular changes have been presented. Autopsy figures from around the world do suggest some change pre and post 1940 (7). London figures early in the 20th century were about 4% and about 12% in the middle of the century; with figures not age standardized the world data are almost incoherent but Scandinavian figures show major rises in the 20th Century.

3. NATURAL HISTORY AND PROGNOSIS

A major issue in the cholelithiasis story is that of its complications and the role of prophylactic cholecystectomy, particularly in the symptom free. We now know that:

1. The majority of people with cholelithiasis are symptom free and will remain so throughout life - about 1-4% annually will develop symptoms, (Table 5)
2. A minority have recurrent attacks of true biliary pain,
3. Carcinoma of the gall bladder, once feared as a complication of stone disease, is a very infrequent occurrence with an incidence of about 1/1000p.a. (13)
4. For obscure reasons gallstones are more likely to produce symptoms in women than men. (4).
5. Symptoms are poor predictors of the presence of gall stones but biliary colic lasting at least 30 minutes and requiring the patient to lie down has moderate predictive value (4).
6. In patients with asymptomatic stone, assuming a complication rate of 2% p.a., 67% will still be asymptomatic after 20 years $(1\text{-}0.02)^{20}$ (12).
7. Those with mild symptoms are more likely to need cholecystectomy eventually than those symptom free (12).
8. The size of gall stones has no bearing on prognosis.
9. There may be two populations of patients with gall stones; a younger group who tend to develop symptoms and require cholecystectomy and a larger older group with a lower tendency to need surgery (4).

The question of prophylactic cholecystectomy for symptomless stone is important and much debated. The available data, however, are sparse and often of doubtful quality. (Table12.2) Before ultrasound there were several studies of the follow up of accidentally discovered gall stones with annual rates of ±2% of problems. On the other hand, follow up of symptomatic patients shows much higher complication rates for those with severe symptoms - 6 - 8 % per annum probably diminishing over the years, whilst for those with mild symptoms complication rates of 1 -3 % are typical. It seems clear that the so-called flatulent dyspepsia is as frequent in people without gall stones as in those with it (14) and that after cholecystectomy for dyspeptic symptoms at least 50% will continue to be symptomatic (15). There is however one clear indication for cholecystectomy in the symptomless patient; the presence of calcification of the gall bladder wall, the so-called ‘porcelain gall bladder’ which is associated with carcinoma in 25% of cases.

It is appropriate to consider the risk and protective factors for gall stones in view of their frequency and the role of cholecystectomy in their management.

Table 5. Natural History of Gall Stones : complication rates

Subjects	**End Point**	**Number**	**Follow-up**	**Rate pa**	**Reference**
Asymptomatic stones at laparotomy	Biliary Colic	112	10-20years	1.4%	8
Slight or no symptoms	Cholecystitis, Jaundice or pancreatitis	95	5-20 years	3% males 6% females	9
Incidental finding	Biliary Colic	123	24 years	1.3%	10
Health Insurance enrollees	Symptoms	135	58 months	2.2%	11
Kaiser Permanente Plan enrollees	Acute cholecystitis jaundice or pancreatitis	123	up to 20 years	±3%	12

4. POSSIBLE RISK FACTORS FOR CHOLESTEROL GALLSTONES

Age
Gender
Parity
The Oral Contraceptive Pill (OCP)
Ethnicity
Obesity
    Type of obesity
Heredity
Smoking
Weight loss
Lack of Exercise

Diet
- Sugar intake
- Dietary cholesterol
- Polyunsaturated fats
- Dietary fibre/constipation

Diabetes Mellitus
Rare Causes
- Rapid weight loss
- Ileal resection
- Colonic resection
- Total Parenteral nutrition
- Drugs

Speculative
- Bacterial infection

5. PROTECTIVE FACTORS FOR CHOLESTEROL GALL STONES

Alcohol
Exercise
Coffee
Non-steroidal anti-inflammatory drugs

6. RISK FACTORS

In general, the major risk factors in western society are age, gender, parity, the OCP, body habitus, dietary factors and low physical activity.

6.1 Age

As already noted, the prevalence of gall stones rises with age, but at a higher rate in females.

6.2 Gender

As noted, throughout the world, the M:F ratio is about 1:2 but in older males, the rise in rate increases towards the female rate.

6.3 Parity

Pregnancy has long been recognised as a risk factor for gall stones based largely on anecdotal evidence but the matter has been clarified by a large Australian study in which 200 women with newly diagnosed gallstones were matched with both community and hospital controls. The risk of gall stones rose with each pregnancy in young women, but the effect was attenuated among older subjects. (16). A remarkable finding was that in 980 young women soon after delivery of a first or second child, stones were found in nearly 12%(<2% in controls) but in 12 of 41 followed up the stones disappeared within six months (17)

6.4 The Oral Contraceptive Pill and Oestrogens

These may represent significant risk factors for cholesterol stone formation. Oestrogen increases biliary cholesterol and diminishes bile acid output, at least in females (18). This may well relate to the increased stone rate in parous women and to the increased rate of cholelithiasis in men with carcinoma of the prostate receiving oestrogens (19). Early studies of the OCP showed an increased incidence of gallstones (OR 2.0;1.4-2.9) in those under 45 years and 2.5 (1.5-4.2) in post menopausal women (20, 21),but with the modern low oestrogen types of pill the risk is small and more evident in younger than older women, an effect mirrored in the effect of pregnancy (22). Once again, a curious finding was that in women younger than 35 years, a higher risk was associated with shorter (<12 months) than with longer exposure.

6.5 Obesity

By far, this is the outstanding risk factor for stone disease in women, both because of its potency and its frequency. In males the relationship, for obscure reasons, is much less evident. One of the most comprehensive studies is from the Nurses' Health Study of 88,837 women aged 34-59 of whom 612 developed gall stones over a four year period (23). A roughly linear relationship was found between relative weight and relative risk of stone. However, it must be recognised that the study, like other cohort studies, only accounted for stones discovered because of symptoms and there are no data on the incidence of symptomless stone in such studies. In the very obese, BMI $\geq$ 32 kgs/m^2, the RR was 6.0 (4-9) compared with those with a BMI < 20. In conformity with an earlier finding by the Adelaide group (16) the study showed that pregnancy had no influence after adjustment for BMI. These findings can only be interpreted as parity being a

risk factor acting only through its effect on weight gain in pregnancy and having no effect *per se*. A later review of eight years experience showed rates of up to 7.4% in the morbidly obese (BMI ≥45 kg/m^2); the annual rates of gall stone symptoms were greater than 1% with a BMI greater than 30 and 2% in those with a BMI greater than 45 (24). Among the numerous other but smaller studies, similar findings were found in women but for totally obscure reasons, not in men, except for two studies of males of Japanese descent (25). The absence of an evident effect in males could be due to the low prevalence and smaller studies but nonetheless the predominant effect in females again raises the issue of a role of oestrogen in lithogenesis, mirroring the evident effect of the OCP. It is now possible to attempt to quantify the contribution of obesity to gall stones in females. If we define obesity as a BMI > 30kg/m^2 when its prevalence is 40% in the population then the Attributable Risk is 28% in that population.

6.5.1 Type of Obesity

There is inconclusive evidence of a doubling of risk in those with central obesity. In a study of men in Bristol, England, the quartile with the highest hip to waist measurement had twice the risk of the lowest but in these men BMI was not predictive. There are however studies both for and against (25).

6.6 Heredity

Long suspected, this has not been adequately studied. An Israeli study of 89 patients with gall stones found a higher prevalence in relatives but the controls were inappropriately older and culturally different. (26). However, a more recent study clarifies the problem. A group of 105 young patients (85F) with gall stones was compared with 105 matched controls. Simultaneously 330 of their first degree relatives were matched with 330 controls. There were 51 relatives with gall stones compared with 12 controls, OR 3.25(2.4-8.5) (27).

6.7 Smoking

This has been poorly studied. In a comparison of 252 cases and age-sex-residence matched controls, gallstones were more prevalent in smokers, especially in women under 35, in whom multivariate analysis showed an OR of 2.8 (1.1-7.1) in those only smoking 1-8 years. (28)

6.8 Weight loss

A likely sequence has been outlined (3). In obesity, bile is supersaturated with cholesterol on account of an elevated cholesterol synthesis and excretion. During caloric restriction, biliary lipid excretion falls as does the size of the bile acid pool. In weight loss bile acid excretion falls more than does cholesterol excretion, possibly due to mobilization of body tissue thus increasing biliary cholesterol saturation. Upon weight stabilization the bile acid pool stabilizes at a high level but the biliary cholesterol does not rise to previous levels.

A more recent report of 47,153 middle aged women in the US Nurses Health Study draws attention of the ill effects of weight cycling, that is, episodes of deliberate weight loss and subsequent regain (Table 6), over a 16 year period.(29)

Table 6. Gallstones and weight cycling

Weight cycle	**% of cohort**	**OR* for cholecystectomy (95%C.I.)**
Maintained weight within 5lb (Reference Group)	11.1%	1.0
5 - 9 lb (2-4kg)	20.1%	1.20(.96 - 1.50)
10-19lb (4.5-8.5kg)	18.8%	1.31 (1.05-1.64)
≥20lb (9kg)	16%	1.68 (1.34-2.10)

*adjusted for B.M.I., age, alcohol intake, fat intake and smoking.

6.9 Exercise

A consistent inverse association between gall stones and physical exercise has been demonstrated both in men (30) and in women (31). Essentially, regular exercise protects against the development of stone. In males under 65 the multivariate RR of stone in the highest quintile of exercise was 0.58 (0.44-0.78), compared with the lowest quintile; in older men the difference was less evident (RR 0.75:0.52-1.08). In men watching television more than 40 hours per week the RR was 3.32 (1.51-7.27) compared to those watching for fewer than 6 hours per week; in younger men the difference was less evident; RR 1.56 (0.38-6.48). In females similar changes were found in the Nurses Health Study. The multivariate RR of cholecystectomy in the highest quintile of physical activity was 0.69 (0.61-0.78). Similarly, sedentary activity was positively correlated with the risk of

cholecystectomy. Women who spent more than 60 hours per week sitting or driving had a multivariate RR of 2.33 (1.26-4.26) even after controlling for body weight. Overall, an average of 2 -3 hours of recreational physical activity weekly reduced the need for cholecystectomy by 20%.

6.10 Alcohol

A role for alcohol, long suspected, has recently been clarified in a cohort study of symptom free men followed for 10 years. (32). Symptomatic stones were diagnosed in 2.4%. After adjustment a clear pattern emerged; a diminished risk of stone was associated with increased amount or frequency of alcohol intake but alcohol intake on 1 - 2 days/ week was ineffective; the nature of the beverage was immaterial. A similar result was found in the Nurses' Health Study in which an intake of at least 5 grams of alcohol per day led to a RR of 0.6 (0.4-0.8) (23).

6.11 Diet

This is probably one of the major risk factors but although extensively investigated, the data are confusing. There is an association with high energy intake in the young with a declining risk with increasing age. Given that the effect of pregnancy, the oral contraceptive, obesity and high energy intake in females are all stronger in younger subjects, it may be that these factors select out susceptibles at an earlier age (33). There are several studies showing a higher calorie intake in gallstone subjects even when matched for sex, body size or exercise status, probably through increased cholesterol output (34).

6.11.1 Sugar

Sugar intake has been implicated but its association with a low fibre diet makes for difficult interpretation. This is unfortunate as there is good evidence that a high fibre diet tends to normalize supersaturated bile. In the Adelaide study, females under 50 with stones had a highly significant elevation of sugar intake; in males under 50 the changes were less evident but still statistically significant. In both males and females over 50 there were no differences nor were any differences found between the groups in dietary fibre intake at all (33).

6.11.2 Vegetarian Diet

In a study of 130 vegetarian women compared with meat eaters and adjusted for age and BMI, the controls had 1.9 times the vegetarians' rate of gallstone (35).

6.11.3 Dietary Cholesterol

In view of the cholesterol content of stones, the dietary intake of cholesterol has been extensively investigated. The evidence for a role for increased cholesterol intake in gall stone formation is weak compared with that for hepatic synthesis, (3).

6.11.4 Polyunsaturated Fat

Evidence on this is sparse. However a recent report from the Health Professionals Follow-up Study in the U.S. finds a role for unsaturated fat in gall stones. Detailed dietary assessments were done at regular intervals from 1986 – 2000 on 45,756 males of whom 2323 developed gall stones (36). After adjustment for potential confounders, a significant protective effect for total unsaturated fat intake (RR=0.82:0.69-0.96) was found comparing the highest with the lowest quintile. The effect was also significant for poly unsaturates and borderline for mono unsaturates. A mechanism proposed is that unsaturated fatty acids when incorporated into cellular membranes lower insulin resistance. As noted earlier, insulin is the main driver of HMG Co A reductase, the rate limiting enzyme in cholesterol synthesis. Whether this relates to the alleged benefits of the "Mediterranean diet" with its reliance on olive oil rather than saturated fat is a matter for speculation.

6.11.5 Coffee

An unusual side effect of coffee intake was revealed in the Health Professionals Follow-Up Study, a prospective study of 46,000 men without gall stones followed over 404,000 person years. During observation 1081 developed symptoms and 885 required cholecystectomy. In those taking ≥ 4 cups of coffee daily, however brewed, the RR was 0.55 (0.32-0.92). The effect was probably mediated by caffeine or a similar chemical as ≥ 800 mg/day intake showed a RR of 0.55 compared to the lower quartile but the decaffeinated coffee was ineffective (37). Similar findings apply to a cohort of 80,898 nurses in a 20 year follow up. For drinkers of ≥ 4 cups daily the RR was 0.72 (P for trend 0.0001). Tea and decaffeinated coffee were ineffective. Calculation of all source caffeine intake confirmed the

association. Strangely, caffeine containing soft drinks which would have been largely cola preparations showed a positive association with gall stones with ≥ 4 cups/ day having a RR=1.41(P trend = 0.003). No explanation for this paradoxical result is evident and it seems not to be related to BMI or the associated sugar intake (38).

6.11.6 Dietary Fibre/Constipation

In spite of the strong association of obesity in females with gall stone disease, there remains a large group of thin women with unexplained gallstones. The Bristol group has investigated this and suggested a link with slow intestinal transit. In 48 females with gall stones, 15 were of normal weight (B.M.I.< 25kg/m^2). Compared with age matched controls, their whole gut transit times were significantly longer (82 versus 63 hours) and stool output lower (74 versus 141 g/day) and the matching was adequate on waist - hip circumference ratio, parity, O.C.P. intake, serum triglycerides and alcohol intake (39). Nearly a century ago Osler (40) drew attention to a possible link of gall stones with constipation. The Bristol group has shown that drug induced constipation made bile more lithogenic with higher deoxycholate levels which up-regulates cholesterol synthesis and favours cholesterol nucleation, while laxative induced diarrhoea had the opposite effect (41). This of course may well be associated with the strong suggestions from the fibre advocates such as Burkitt and Cleave, that the high fibre diet of tribal Africans is the reason for their relative immunity from gall stones. However, the fibre hypothesis for gall stone aetiology does not explain the rarity of gall stones in primitive Eskimos on a carnivorous diet nor of the tribal Masai on a diet of blood and milk.

6.12 Diabetes Mellitus

Although there has long been a view that diabetes mellitus is associated with gall stones, evidence in support is very sparse (22, 42). However complications such as cholecystitis and cholecystectomy pose a greater hazard in diabetic patients.

6.13 Rare Causes

These include rapid weight loss, ileal resection, total parenteral nutrition and drugs.

6.13.1 Rapid Weight Loss

Of obese people 10 - 25% will develop gallstones within months of severe dieting with up to one in three developing symptoms with the risk proportional to the degree of obesity and to the rate of weight loss. The administration of ursodeoxycholic acid prevents the phenomenon (25). The risk is even greater after gastric bypass surgery, with gall stones developing in 38% within 18 months of such surgery. In summary about 1 in 3 people with major weight loss from dietary or obesity surgery develop gall stone symptoms; but about half of the stones spontaneously disappear over one or two years (25). There are no data on the effect of differing compositions of dietary regimens, nor are there data comparing smaller frequent meals with conventional eating times. The practical lesson is that in the obese, particularly in those with those with raised serum triglyceride levels, rapid weight loss regimens should be avoided. Ursodeoxycholic acid prevents stone formation but its long term use is very expensive. Allied to this is the nature of the fasting regimen; those who fast 14 hours overnight had a doubling in their risk compared with those fasting less than 8 hours. Perhaps the longer fast contributes to a greater concentration and amount of gall bladder bile.

6.13.2 Ileal Resection

This is a risk factor for gall stone formation, but the ability of the liver to increase bile acid synthesis is considerable and the risk remains low with resection of less than 100cm (43).

6.13.3 Total Parenteral Nutrition

This also is associated with gallstone formation, almost certainly in part due to lack of stimulation of gall bladder contraction and reduced cycling of bile acids.(44).

6.13.4 Drugs

There are a number of drugs associated with gallstone formation.

6.13.4.1 Clofibrate

Widely used for heart disease in the recent past this raises biliary cholesterol output and saturation with an increased incidence of gallstones.

6.13.4.2 Bile acid sequestrants

Cholestyramine and Colestipol do not of themselves increase gallstone incidence but given with Clofibrate make bile more lithogenic.

6.13.5 Bacterial infection

A bacterial aetiology for cholesterol stones has been speculated, recognising the clear evidence for infection in pigment stones in East. A novel approach using modern molecular biology has been fruitful. Bacterial gene fragments amplified from DNA extracted from cholesterol stones were found in 16 of 17 mixed cholesterol patients. However, none were found in stones with >90% cholesterol from three patients. Three bacterial types were identified, propionibacteria, enterobacteria and a mixed group of gram-positive organisms (45). The role of bacteria in cholesterol stone formation remains speculative.

7. PROTECTIVE FACTORS FOR CHOLESTEROL STONES

Exercise:
Coffee:
Vegetarian Diet:
Alcohol:
} see above

Non-steroidal anti-inflammatory drugs.(NSAIDs).

Remarkably, there is evidence that regular intake of NSAIDs protects against stone, not only in animals on a lithogenic diet, but in humans. In 75 patients who had their gall stones dissolved with ursodeoxycholic acid, and followed for 33 months none of the 12 regular NSAID users had stone recurrence, compared with 20 of the 63 rare or never users, OR=.08 (.005-1.5)(46). The topic cries out for further investigation.

Whilst the vast majority of epidemiological studies treat gallstones collectively, we need to be reminded that there are three major types of gallstones differing in nearly all respects and that the epidemiological data implicitly refer to cholesterol stone and conclusions about causation will tend to be confounded by the different pigment stones in the west. The problem of gallstone cause and treatment gains extra relevance in view of the growing epidemic of obesity, particularly in the US from which we can expect an epidemic of gallstones for which no practical preventive measures are available, unless NSAIDs prove to be effective.

Two issues become clear. Firstly, the data indicate that there are probably two populations of stone formers; a minority group of young

women who, exposed to pregnancy, the OCP or smoking will rapidly risk stone development and the majority group in whom the risk of stone becomes evident in later life with less evidence of exogenous factors.

The second issue is the lack of a unifying hypothesis to integrate the action of the numerous modifying factors discussed above. The common explanation of cholesterol crystallization as originating in supersaturated bile explains nothing. An equally important question is why more people in the west don't get stones. Supersaturated bile is frequent in western societies; obese males are as likely to have supersaturated bile as obese females but less likely to develop stones. Many people apparently have trouble free courses in spite of supersaturated bile for long periods.

References

1. Arnaud JP, Aprahamian M, Eloy MR, Adloff M. The x-ray diffraction pattern of gallstones: identification of pure mineral stones. *Br. J. Surg.* **65**,362 (1978).
2. Solway RD, Trotman BW, Ostrowj D, Pigment gallstones. *Gastroenterology* **72**,167-182 (1977).
3. Bennion LJ, Grundy SN. Risk factors for the development of cholelithiasis in man. *N. Engl. J. Med.* **299**,1161-7 and 1221-7 (1978).
4. Heaton KW, Bradden FEM, Mountford RA, Hughes AO, Emmett PM. Symptomatic and silent gall stones in the community. *Gut* **32**,316-20 (1991).
5. Sampliner RE, Bennett PH, Comess LJ, Rose FA, Burch TA. Gallbladder disease in Pima Indians. Demonstration of high prevalence and early onset by cholcystography. *N. Engl. J. Med.* **283**,1358-64 (1970).
6. Lowenfels AB. Gallstones and the risk of cancer. *Gut* **21**,1090-92 (1980).
7. Brett M, Barker DJP. The world distribution of gallstones. *Int. J. Epidemiol*. **5**,335-41 (1976).
8. Comfort MW, Gray HK, Wilson JM. The silent gallstone: a ten to twenty year follow-up study of 112 cases. *Ann. Surg.* **128**,931-7 (1948).
9. Lund J. Surgical indications in cholelithiasis: proplylactic cholecystecomy elucidated on the basis of long term follow up on 526 non-operated cases. *Ann. Surg.* **15**1,153-61 (1960).
10. Gracie WA, Ransohoff DF. The natural history of silent gall stones: the innocent gallstone is not a myth. *N. Engl. J. Med.* **3007**,789-800 (1982).
11. McSherry CK, Ferstenberg H, Calcoun WF, Lahman E, Virshup M. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. *Ann. Surg.* **202**,59-63 (1985).
12. Friedman ED. Natural history of asymptomatic and symptomatic gallstones. *Am. J. Surg.* **165**,399-404 (1993).
13. Maringhini A, Moreau JA, Melton LJ, Hench VS, Zinmeister AR, DiMagno EP, Gallstones, gallbladder cancer and other gastrointestinal malignancies: an epidemiological study in Rochester, Minnesota. *Ann. Int. Med.* **107**,30-5 (1987).
14. Jorgensen T. Abdominal symptoms and gallstone disease: an epidemiological investigation. *Hepatology* **9**,856-61 (1989).
15. Ros E, Zambon D. Post-cholecystectomy symptoms. A prospective study in gall stone patients before and over two years after cholecystectomy. *Gut* **28**,150-4 (1987).
16. Scragg RK, McMichael AJ, Seamark RF(b). Oral contraceptives, pregnancy and endogenosis oestrogen in gall stone disease - a case-control study. *Br. Med. J.* **288**,1795-9 (1984)

17. Valdiviesco V, Covarrubias C Siegel F et al. Pregnancy and cholelithiasis: pathogenesis and natural course of gallstones diagnosed in early puerperium. *Hepatology* **17**,1-4 (1993).
18. Bennion LJ, Ginsberg RL, Ganick MB et al. Effects of orgal contraceptives on the gall bladder bile of normal women. *N. Engl. J. Med* .**294**,189 (1976).
19. Henrickson P, Einarsson K, Eriksson A. Estrogen - induced gallstone formation in males. *J. Clin. Invest*. **84**:811-816 (1989).
20. Boston Collaborative Drug Surveillance Program. Oral Contraceptives and venous thromboembolic disease: Surgically confirmed Gallbladder disease and breast tumours. *Lancet* **1**,1399-1404 (1973).
21. Boston Collaborative Drug Surveillance Program. Surgically confirmed Gallbladder disease, venous thromboembolism and breast tumours: relation to postmenopausal therapy. *N . Engl. J. Med.* **290**,15-19 (1974).
22. Diehl AK, Epidemiology and natural history of gall stone disease. *Gastroenterol.Clin. N. Am* . **20**,1-19 (1991).
23. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet and the rest of symptomatic gallstones in middle-aged women. *N. Engl. J. Med.* **321**,5463-9 (1989).
24. Stampfer MJ, Maclure KM, Colditz CA, Manson JE, Willett WC. Risk of Symptomatic gallstones in women with severe obesity. *Am. J. Clin. Nutr.* **55**,652-8 (1992).
25. Everhart JE, Contributions of obesity and weight loss to gallstone disease. *Ann. Intern. Med.* **119**,1029-35 (1993).
26. Gilat T, Feldman C, Halpern Z, Dan M, Bar-Meir S. An increased familial frequency of gallstones. *Gastroenterology* **84**,242-6 (1983).
27. Sarin SK, Negi VS, Dewan R et al. High familial prevalence of gallstones in first-degree relatives of gallstone patients. *Hepatology* **22**,138-141 (1995).
28. McMichael AJ, Baghurst PA, Scragg RK. A case-control study of smoking and gallbladder disease:importance of examining time relations. *Epidemiology* **3**,519-22 (1992).
29. Syngal S, Coakley EH, Willett WC, Byers T, Williamson DF, Colditz GA. Long term weight patterns and risk for cholecystectomy in women. *Ann. Intern. Med.* **130**,471-7 (1999).
30. Leitzmann MF, Giovannucci EL, Rimm EB et al. The relation of physical activity to risk for symptomatic gallstone disease in men. *Ann. Intern. Med* . **128**,417-25 (1998).
31. Leitzmann MF, Rimm EB, Willett WC et al Recreational physical activity and the risk of cholecystectomy in women. N .Engl. J. Med. **341**,777-84 (1999).
32. Leitzmann MF, Giovannucci EL, Stampfer MJ et al.Prospective study of alcohol consumption patterns in relation to symptomatic gallstone disease in men. *Alcohol. Clin. Exp. Res.* **23**,835-41 (1999).
33. Scragg RK, McMichael AJ, Baghurst PA.(a) A Diet, alcohol and relative weight in gall stone disease: a case-control study. *Br. Med. J.* **288**,1113-9 (1984).
34. Sarles H, Crotte C, Gerolami A et al. The influence of calorie intake and of dietary protein on the bile lipids. *Scand. J. Gastroenterol.* **6**(18), 191 (1971).
35. Pixley F, Wilson D, McPherson K et al. Effect of vegetarianism on development of gallstones in women. *Br .Med. J.* **291**,11-13 (1985).
36. Tsai C-J, Leitzmann MF, Willett WC, Giovannucci EL. The effects of long-term intake of unsaturated fats on the risk for gallstone disease in men. A prospectice cohort study. *Ann. Intern .Med.* **141**,514-22 (2004).

37. Leitzmann MF, Willett WC, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. *JAMA* **28**,2106-12 (1999).
38. Leitzmann MF, Stampfer MJ, Willett WC, Spiegelman D, Colditz GA, Giovannucci EL. Coffee intake is associated with lower risk of symptomatic gallstone disease in women. *Gastroenterology* **123**,1823-30 (2002).
39. Heaton KW, Emmett PM, Symes CI. et al An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet* **341**,8-10 (1993).
40. Osler, W. Cholelithiasis in: *The Principles and Practice of Medicine*.7th Edn. (Appleton and Co, New York and London, 1909), p.548.
41. Marcus SN, Heaton KW. Intestinal transit, deoxycholic acid and the cholesterol saturation of bile: three inter-related factors. *Gut* **27**,550-8 (1986).
42. Heaton KW. The epidemiology of gall stones and suggested aetiology. *Clin. Gastroenterol.* **2**,67-83 (1973).
43. Hill GL, Mair WSJ, Goliger JC. Gallstones after ileostomy and ileal resection *Gut* **16**,932-6 (1975).
44. Roslyn JJ, Pitt HA, Mann LL et al. Gallbladder disease in patients on long-term parenteral nutrition. *Gastroenterology* **84**,148 (1987).
45. Swidsinski A, Ludwig W et al. Molecular genetic evidence of bacterial colonization of cholesterol gallstones. *Gastroenterology* **108**,860 (1995).
46. Hood K, Gleeson D, Ruppin DC, Dowling RH. Prevention of gall-stone recurrence by non-steroidal anti-inflammatory drugs. *Lancet* **2**,1223-5 (1988).

Chapter 11k

CHOLANGIOCARCINOMA

1. DESCRIPTIVE EPIDEMIOLOGY

Bile duct tumours (cholangiocarcinomas) are a rare tumours arising from the biliary tree. Like HCC there is wide geographic variation in incidence with higher prevalence found in areas where liver fluke infestation is endemic. Overall cholangiocarcinoma is far less common than HCC and only accounts for about 3% of all gastrointestinal tumours in the West. The ICD 10AM Code C22.1. Like HCC cholangiocarcinomas usually present late and for this reason are highly lethal. In the majority of cases no cause has been identified but for the minority, risk factors include long standing developmental abnormalities of the biliary tree. They also complicate longstanding sclerosing cholangitis. In Far East there is a high incidence of cholangiocarcinoma linked to a high prevalence of chronic liver fluke infestation of the biliary tree with Clonorchis sinensis and Opisthorchis viverrini, known risk factors for this malignancy.

2. PREVALENCE

Cholangiocarcinomas are rare in the West with a prevalence in autopsy studies of less than 1% (1). The incidence of cholangiocarcinoma may be rising in the US, UK and Australia (2). Better diagnostic techniques cannot account fully for this rise.

3. NATURAL HISTORY

Jaundice secondary to outflow obstruction of the biliary system is a frequent first presentation. Thus prognosis is very poor with a median survival of 5 months (3).

4. ASSOCIATIONS

Chronic inflammation and injury of the biliary epithelium is the proposed mechanism for its development in many of the conditions associated with the cancer. Congenital malformations are associated with cholangiocarcinoma. The most frequently associated are choledochal cysts which are associated with chronic bile stasis. The risk is estimated at 10% overall with risk increasing with duration of disease. Congenital anomalous junction of the pancreatobiliary tree is also associated with reflux of pancreatic juices into the biliary tree and cholangiocarcinoma. Caroli's disease is a congenital disorder characterized by multifocal, segmental dilatation of large intrahepatic bile ducts. The risk of cholangiocarcinoma is increased (up to 7 percent), probably due to the significant bile stasis and the presence of high concentrations of unconjugated secondary bile salts. Both cholelithiasis and hepatolithiasis have been implicated in the pathogenesis of cholangiocarcinoma but the evidence is poor in the absence of coexisting parasitic infestation.

Two genetic disorders associated with adenoma/ carcinoma development are associated with cholangiocarcinoma. These are Lynch syndrome II, and multiple biliary papillomatosis, a rare disorder with a high incidence of malignant transformation.

Primary sclerosing cholangitis (PSC), characterized by stricturing, fibrosis and inflammation of the biliary tree is associated with cholangiocarcinoma in up to 20% of patients.

It is estimated that the relative risk of developing cholangiocarcinoma in UC is elevated 20-30 times. Colectomy does not protect against cancer development and can occur many years later.

5. AGE AND GENDER

Cholangiocarcinoma affects the older population (50-70 years except when the disease is associated with sclerosing cholangitis and choledochal cysts and presentation can be up to 2 decades earlier (1). There is no clear gender difference.

6. GEOGRAPHY

The incidence of cholangiocarcinoma is highest where liver fluke is endemic such as Thailand and Hong Kong.

7. EFFECTS OF INTERVENTION

There is no known effective intervention. Liver transplant does not protect against tumour recurrence.

8. SUMMARY

Except in regions where liver fluke is endemic cholangiocarinoma is a rare cause of GI cancer of largely unknown aetiology. While there is a recognised association with congenital abnormalities of the biliary system such as choledochal cysts and with PSC these are unmodifiable risk factors and thus in the absence of fluke infestation no effective preventative strategies are known for this disease.

References

1. Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. Semin. *Liver Dis.* **14**(2),109-14 (1994).
2. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* **33**(6),1353-7 (2001).
3. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ Jr, LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann. Surg.* **213**,21-5 (1991).

Chapter 12

ALCOHOL AND THE GUT

It is not widely recognised that alcohol in excess has the capacity to produce, not only structural, but also significant changes in gut function. It is proposed to review these changes recognizing that some have already been canvassed fully in previous chapters. The changes may be summarized as occurring in :

- The parotid gland
- Pharynx
- Café Coronary (sudden restaurant death syndrome)
- Oesophagus – squamous cell carcinoma and rupture of oesophagus
- Stomach – gastritis and Mallory-weiss lesions
- Pancreas – pancreatitis and adenocarcinoma
- Small bowel absorptive defects
- Liver – structural changes
- metabolic changes
- Colon – structural changes – rectal abscess
- functional – morning diarrhoea

1. PAROTID GLANDS

This is one of the few changes evident to the casual observer. Less than 50 years ago attention was drawn to the bilateral symmetrical swelling of the parotids which is largely confined to heavy drinkers and is strongly associated with alcoholic liver disease (1, 2). The pathology is not well described but some show fatty infiltration and others are normal. The condition is not unusual in TV interviews of prominent community members.

2. PHARYNX

According to the International Agency for Research on Cancer (IARC), alcohol is causally related to cancer of the oral cavity and larynx but not to nasopharynx (3).

3. CAFÉ CORONARY (SUDDEN RESTAURANT DEATH SYNDROME)

Attention was drawn to this in a report of 1963 "a middle aged or elderly person, at a fashionable restaurant is partaking of fillet mignon, or perhaps broiled lobster or prime beef. At the same time, he is conversing with companions at dinner. Suddenly he ceases to eat and talk. The dinner companions are perplexed but not alarmed because there is no indication of distress. Then the person suddenly collapses at the table. Attempts at resuscitation are made…" At the hospital emergency room he is pronounced dead (4). The cause is impaction of sometimes a remarkably large piece of meat. Subsequently the National Safety Council of the US estimated that nearly 2500 such fatalities occur in the US annually (5). "Acute alcoholism, poor teeth and atrocious table manners are considered to be the precipitating factors" (5).

4. MALLORY-WEISS LESION

These, which constitute up to 7% of admissions for acute upper gastrointestinal bleeding are most often due to the vigorous vomiting from alcohol abuse producing a linear tear at the cardia and lower end of the oesophagus. Minor degrees are fairly common.

5. MORGAGNI'S SYNDROME

This, also due to vigorous vomiting, is a rare condition when a tear in the lower oesophagus extends through the wall to empty the gastric contents into the pleural sac with fatal consequence unless rapid diagnosis and surgery are achieved.

6. SQUAMOUS CARCINOMA OF THE OESOPHAGUS

See Chapter 4b.

7. GASTRITIS

See Chapter 5b.

8. PEPTIC ULCER

See Chapter 5a.

9. PANCREATITIS

See Chapter 5.

10. SMALL BOWEL ABSORPTIVE DEFECT

Although there is no evidence of structural changes in the small gut from alcohol, there is some evidence of absorptive defects. In a study of 29 heavy drinkers, 27 had one or more absorptive defects in an uncontrolled study. Around half the patients had excessive faecal fat and nitrogen and B12 absorption and d-xylose absorption were defective in three quarters suggesting a jejunal defect. Unfortunately a contribution from pancreatic defect could not be excluded in the changes (6). In a study of 37 cirrhotic alcoholics and 12 healthy controls, the cirrhotics had significant depression of thiamine, pyridoxine and polylpolyglutmate but synthetic folic acid absorption was normal (7). Such findings resonate with the deficiency of thiamine and folate often seen in alcoholism (8).

11. LIVER – METABOLIC CHANGES

Apart from the profound structural changes in the liver from alcohol, there are also wide spread functional changes not clearly attributable to these (9). These include :

- Depressed gluconeogenesis which may manifest as hypoglycaemia
- Raised serum triglycerides
- Increased lactate production leading to urate retention and gout
- Increased catecholamine release depressing β adrenergic receptor activity.
- Hypermetobolic state – "empty calories"
- Hypertension

12. COLON

Rectal adenocarcinoma (see Chapter 8a).

13. MORNING DIARRHOEA

Not well recognised is the morning diarrhoea of the alcohol abuser, the so called "morning squirts", with several rapid liquid evacuations on arising. It is not well investigated but it has been speculated that the passage of non absorbable carbohydrate in beer from fermented grain in the colon is causative.

References

1. Brick IB. Parotid enlargement in cirrhosis of the liver. *Ann.Intern. Med.* **49**,438-451 (1958).
2. Duggan JJ, Rothbell EN. Asympatomatic enlargement of the parotid glands. *N. Engl. J. Med.* **257**,1262-7 (1957).
3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. IARC monographs on the evaluation of carcinogenic risks to humans, no, 44. *Alcohol drinking.* (International Agency for Research on Cancer, Lyons, 1988), pp.249-260.
4. Haugen RK. The Café Coronary. Sudden deaths in restaurants. *JAMA* **186**,142-4 (1963).
5. Euler WC, Haugen RK. Food asphyxiation in restaurant rescue. *N. Engl. J. Med.* **289**,81-2 (1973).
6. Roggin GM, Iber FL, Kater RHM, Tabon T. Malabsorption in the chronic alcoholic. *Johns Hopkins Med. J.* **125**,21-330 (1969).
7. Baker H, Oscar F, Zetterman RK, Rajan KS, Hove W, Leevy CH. Inability of chronic alcoholics with liver disease to use food as a source of folate, thiamine and vitamin B6. *Am. J.Clin. Nutr.* **28**,1377-1380 (1975).
8. Wu A, Chanarin I, Slavin G, Levi AJ. Folate deficiency in the alcoholic – its relationship to clinical and haemoatological abnormalities, liver disease and folate stores. *Br. J. Haematol.* **29**,469-478 (1975).
9. Isselbacher KJ. Metabolic and hepatic effects of alcohol. *N. Engl. J. Med.* **269**,612-6 (1977).
10. Duggan JM, Dobson A. A mathematical view of alcohol and drug use. *Aust. Drug Alcohol Rev.* **1**,71 (1982).

Chapter 13

THE GUT IN AIDS

1. OVERVIEW

AIDS, the Acquired Immuno Deficiency Syndrome is caused by a virus, a retrovirus of unknown biologic origin. This virus selectively attacks the T lymphocytes of the CD 4 type and any cell with the CD 4 cell surface marker. Until the development of quite effective antiviral therapy in the late 1990's, the so called HAART (Highly Active Antiretroviral Treatment) drug regimens, the syndrome was regarded as uniformly fatal. This was most often because of the almost inevitable opportunistic infections, frequently affecting the gut and lungs with strange or unusual organisms, difficult or impossible to treat. Given the high cost of HAART therapy, its use is largely confined to the affluent west. In the undeveloped world the magnitude of the AIDS problem is horrifying in its effects, not only on individuals, but on the societies concerned. Appropriate retroviral therapy has largely prevented or aborted the infective complications previously seen and two aspects are worth brief review:

- The gut complications seen before this therapy was developed and in those areas where it is not readily available.
- The not insignificant liver complications of the syndrome and its therapy.

2. THE GUT COMPLICATIONS IN THE UNTREATED (1).

These are predominantly:

- Cytomegalovirus infections of the mouth, oesophagus and colon. These produce stomatitis, odynophagia, dysphagia and a most disabling diarrhoea.
- Candida likewise can affect the mouth, oesophagus and rectum. Ultimately nearly all terminal AIDS patients develop candida stomatitis.
- Cryptosporidia which can cause an intractable diarrhoea.
- Cyclospora which shows some similarity to cryptosporidia.
- Microspora species – very small organisms recognised as common pathogens in AIDS.
- It is evident that with difficulty in eating and swallowing and diarrhoea, the story of AIDS is so often a terminal wasting disorder. For obscure reasons G lamblia and E histolytica infections are not increased in prevalence in AIDS.
- Infection with the standard enteric pathogens is also common – salmonella, shigella, Campylobacter as is Cl difficile infection as a response to the high usage of oral antibiotics in AIDS. The raising of the CD4 lymphocyte count with appropriate therapy is often dramatically beneficial in these patients where drugs to inhibit the organisms are often lacking. Kaposi's sarcoma and non hodgkin's lymphoma can occur almost anywhere in AIDS including the gut.

3. LIVER DISEASE

Liver disease in treated AIDS patients may result either from the infection or from the therapy. Parenchymal liver disease attributable to drugs, either prescribed or not, is the commonest cause of abnormal liver function tests in AIDS. Mycobacterial infection with either M. tuberculosis or M. avium species may affect either the gut or the liver. Recurrence of Hepatitis B infection in those regarded as cured occurs and co-infection with Hepatitis B and Hepatitis C together with HIV are frequent. The coincidence of HIV and chronic Hepatitis B carrier state is not uncommon and with the initiation of HAART in such patients there may be a dramatic flare up in the hepatitis.

Viral and protozoal infections of the liver are common especially Histoplasma, Candida, Cryptococcus; Kaposi's sarcoma and Non Hodgkins lymphoma are also frequently seen.

It is clear that HAART therapy has totally changed the picture of AIDS and that the treatment has the capacity to raise the CD 4 cell count to levels where the risk of these infective complications is minimal. As a result there is clear evidence of a fall in the incidence of these infections during the late 1990's following the widespread use of such therapy(2).

References

1. Wilcox CM. Gastrointestinal consequences of infection with human immunodeficiency virus in : Feldman M, Friedman LS, Sleisinger MH, eds. *Sleisinger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, diagnosis, management.* 7th Ed. (Saunders, Philadalphia, 2002), vol. 1, pp. 487-506.
2. Kaplan JE, Hanson D, Dworkin HS et al. Epidemiology of human immunodeficiency virus – associated opportunistic infections in the United States in the era of highly active retroviral therapy. *Clin. Infect. Dis.* **30** (Suppl 1),S5-14 (2002).

Chapter 14

THE GUT IN SYSTEMIC DISORDERS

1. DIABETES MELLITUS

There are two principal gut complications of diabetes mellitus. These are:

- Diabetic autonomic neuropathy
- Oesophageal candidiasis

Diabetic autonomic neuropathy is a common, serious and often intractable complication especially seen in elderly patients with long standing insulin dependent diabetes mellitus. Evidence of poor diabetic control and neuropathy, both cardiovascular and peripheral, are common. The pathogenesis is not entirely clear and it affects the sympathetic more than the parasympathetic (vagal) system. The manifestations depend upon the site principally affected but in a typical case, widespread abnormalities may be found, even if symptomless, attributable in part to the sensory neuropathy also present. The principal sites of affect and symptoms are :

- Oesophagus. Disturbances of oesophageal motor activity are frequent, often together with gastroparesis and symptoms are present in a minority of patients.
- Stomach. Gastroparesis is said to affect more than half of such diabetic patients. Motility is diminished and emptying of solids is greatly disturbed although liquid may be handled normally. In diabetics hyperglycaemia inhibits gastric emptying but there is also a major depression of vagal function in gastroparesis. Not only may the condition be associated with bloating, fullness after meals, early satiety and post-prandial vomiting, but the impaired gastric emptying

complicates diabetic control. As with other forms of diabetic neuropathy, drug treatment is unsatisfactory.

- Diabetic Diarrhoea. This is common in people with diabetic autonomic neuropathy and is particularly evident in type 1 diabetics with diabetic gastroparesis. Often associated with steatorrhoea of unclear origin it is characterised by nocturnal diarrhoea which may be intermittent and even alternate with periods of constipation. Management is very difficult with strict diabetic control central to treatment. Faecal incontinence, constipation, even culminating in megacolon or pseudo obstruction and abdominal pain of obscure origin may also occur.

2. AMYLOID DISEASE

There are a number of disorders in which deposits of this strange glycoprotein with unique staining characteristics on microscopic examination occur with subtle differences in the chemical nature of the protein involved. All may affect the gut, principally infiltrating the blood vessel walls, smooth muscle of the intestine and muscularis mucosa which may cause malabsorption. Any part of the gut may be involved from the tongue, causing macroglossia, oesophagus causing motility problems, gastric changes leading to motility problems or mechanical obstruction, small bowel causing malabsorption or pseudo obstruction. Bleeding may occur from the fragile involved vessels and the liver may be greatly enlarged by amyloid infiltration. Amyloid is often found diffusely elsewhere; whilst rectal biopsy has been the traditional method of diagnosis, less invasive approaches such as subcutaneous or duodenal biopsy often provide the answer. The treatment is, in general, ineffective.

3. COLLAGEN VASCULAR DISORDERS

These, in themselves a melange of complex disorders of varying frequency, are nearly all associated with gastrointestinal complications. Some, such as the cholecystitis and appendicitis of polyarteritis nodosa are relatively specific to the prime condition. Others may be considered general being associated with a variety of collagen vascular disorders. It is not intended to cover the large area which has little epidemiological interest but it may be appropriate to consider some of the main issues which really boil down to :

- Smooth muscle effects
- Vasculitis

- Side effects of Treatment

1. Smooth Muscle Effects. These are frequently seen in scleroderma; nearly all patients have disordered oesophageal motility with dysphagia and reflux oesophagitis from cardiooesophageal sphincter disturbance is close to universal. Smooth muscle atrophy and fibrosis impair gastric and small bowel structure and function even leading to malabsorption, and constipation from colonic involvement is frequent. On the other hand, while laboratory evidence of impaired oesophageal motility in rheumatoid arthritis is frequent, symptoms are rare. Oesophageal problems incur in most of the other collagen vascular disorders such as SLE and Sjogren's syndrome.
2. Vasculitis. This is frequently seen in these disorders and may provoke a remarkable variety of changes – abdominal pain, bleeding, cholecystitis, bowel stricture and infarction, perforation and pancreatitis. Diagnosis can be very difficult because it is a small vessel vasculitis and a fatal outcome may ensue.
3. Side Effects of Treatment. May of these disorders are treated by potent regimes with a major potential for GI side effects. Numerically, NSAIDs, widely used in rheumatoid arthritis predominate with their gastro duodenal effects (Chapter 5a) but also small bowel and even colonic ulcer and stricture formation may occur. The other major drug classes are the anti metabolites. Methotrexate is widely used in rheumatoid arthritis but has the potential to produce a largely silent hepatitis and even cirrhosis, generally limiting total dosage. Corticosteroids are widely used with the possibility of an enormous list of side effects. In the gut a significant problem is the increased risk of ulcer and death in patients concurrently receiving corticosteroids and NSAIDs.

4. FIBROCYSTIC DISEASE OF THE PANCREAS – CYSTIC FIBROSIS

This is one of the most frequent of the lethal genes affecting humans with a prevalence of around 1 in 3000 white American neonates but only one fifth of this figure in African American and one tenth of it in Asians. The disease is very rare in Japanese. Its basis is a recessive disorder due to any one of numerous mutations of the CFTR gene on chromosome 7 which concerns itself with a protein governing chloride channels at the cell membrane. There is also evidence of modifier genes on chromosome 19 so that a variety of phenotypes are seen. Characteristically, the mutation causes a raised viscosity dysfunction of exocrine secretion with major effects on lungs producing chronic infection or emphysema, pancreas producing pancreatitis,

pancreatic insufficiency and malabsorption, raised sweat chloride levels and male infertility. Previously a disease largely associated with a brief life in children, with modern methods of countering the pulmonary infection survival into adult life is now common and around half of the sufferers reach their 30th birthday with the development of new syndromes : diabetes type 2 from involvement of the islets of Langerhans and from the GI point of view, biliary cirrhosis around puberty with portal hypertension. There is throughout life a risk of bowel complications, from meconium ileus in the neonate and intestinal obstruction later on, even into adult life from the viscous state of bowel contents and pancreatic insufficiency. Ashkenazi Jews tend to have a characteristic mutation. Drug therapies mainly centre on pancreatic extracts to improve nutritional state, fat soluble vitamins for the malabsorption and on the intractable pulmonary infection.

5. ALPHA 1 ANTITRYPSIN DEFICIENCY

The alpha 1 antitrypsin protein is normally secreted by the liver into the blood stream as one of the family of anti proteases which inhibit neutrophil proteases and elastases. The disease, an autosomal recessive disorder due to a variety of defects in the gene on chromosome 14 causes the accumulation of an abnormal protein within the liver cell with the potential to cause a chronic hepatitis, cirrhosis, portal hypertension and even hepatocellular carcinoma. The homozygote is also at risk of emphysema in those that escape the main impact on the liver, and in those exposed to tobacco smoke, life threatening emphysema may develop. The disorder is not uncommon. In a large Swedish study of 200 000 neonates, 127 were found to have the Pi (protease inhibitor) ZZ genotype, the common one producing the abnormal ZZ type protease. Of these 14 had cholestatic jaundice, 9 had severe liver disease but only about half had abnormal liver function tests and the 127 with jaundice tended to improve in childhood so only a minority of 5-10% developed chronic liver disease. There are other alleles, some of which do not lead to chronic liver disease and heterozygotes do not develop liver disease. The major variation in clinical presentation in liver and lung pathology supports the proposition that, once again, modifier genes have a part in the development of the phenotype.

Index