PROGRESS IN SURGICAL PATHOLOGY

Volume V

Edited by

Cecilia M. Fenoglio, M.D.

Marianne Wolff, M.D.

Progress in Surgical Pathology

☐ VOLUME V

Edited by

Cecilia M. Fenoglio, M.D.
Professor of Pathology
University of New Mexico
Director of Laboratory Services
Albuquerque Veterans Administration Medical Center
Albuquerque, New Mexico

Marianne Wolff, M.D.
Professor of Clinical Surgical Pathology
Columbia University College of Physicians and Surgeons
Department of Pathology
Memorial Hospital
Morristown, New Jersey

MASSON Publishing USA, Inc.
New York • Paris • Barcelona • Milan • Mexico City • Rio de Janeiro

ISBN 0-89352-198-1

Library of Congress Catalog Card Number 80-80334

Printed in the United States of America

Preface

This series *Progress in Surgical Pathology* was originally inspired by and dedicated to a man who has spent, and still spends, his life devoted to the practice of surgical pathology. The initial four volumes were the product of invitations to physicians from all over the world, all of whom had interacted with Dr. Lattes to varying degrees and from various vantage points. The articles which resulted from these invitations speak for themselves for, since their publication, the books have sold well. All of the proceeds of the volumes have been donated to resident training, teaching, and research. More importantly, we have been approached by an international array of authors who have sent unsolicited manuscripts to be considered for publication in this series. In that connection, we wish to point out that at least two, and often more, reviewers scrutinize each manuscript and, unfortunately, some offerings must be rejected for publication.

In the future, in order to maintain the flexibility and content of the series, we will continue to consider manuscripts which are philosophical, historical, or basic science in content as well as the more traditional surgical pathology type of manuscripts. In general, we will not accept isolated case reports, since ours is not a journal in the strictest sense.

For the present, it will be our continuing policy to turn the royalties earned by the series into activities that involve teaching, research, and developing new diagnostic services.

Cecilia M. Fenoglio, M.D.

Marianne Wolff, M.D.

Contributors

Aaron Chevinsky, B.S., College of Physicians and Surgeons, Columbia University, New York, New York 10032

Diane W. Crocker, M.D., Professor of Pathology, University of Tennessee Health Center, Memphis, Tennessee

John J. Fenoglio, Jr., M.D., College of Physicians and Surgeons, Columbia University, New York, New York 10032

Jean Hurlimann, M.D., Professor of Pathology, Institute of Pathology, 1011 Lausanne, Switzerland

Jay Lefkowitch, M.D., Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Kevin O. Leslie, M.D., Department of Pathology, University of Colorado Health Sciences Center, Denver, Colorado

Cecile Leuchtenberger, Ph.D., M.A., formerly, Head, Cytochemistry Department, Swiss Institute for Experimental Cancer Research, 1066 Epalinges, Switzerland

Ricardo Mesa-Tejada, M.D., Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York, 10032

Gary J. Miller, M.D., Ph.D., Department of Pathology, University of Colorado Health Sciences Center, Denver, Colorado 80262

Luciano Ozzello, M.D., Professor of Surgical Pathology, College of Physicians and Surgeons, Columbia University, New York, New York, 10032

Conrad L. Pirani, M.D., Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York, 10032

Hans Skovgaard Poulsen, M.D., The Danish Cancer Society, The Institute of Cancer Research, Radiumstationen, DK-8000 Aarhus C, Denmark

Wofgang Remmele, M.D., Director, Institute of Pathology, 6200 Wiesbaden, Federal Republic of Germany

Stephen G. Romansky, M.D., Department of Pathology, St. Jude Hospital, Fullerton, California 92634

Stephen F. Ryan, M.D., Chief of Anatomic Pathology, St. Luke's-Roosevelt Hospital Center, New York, New York 10025 and College of Physicians and Surgeons, Columbia University, New York 10032

Fred G. Silva, M.D., The University of Texas Health Science Center at Dallas, Dallas, Texas 75235

Steven G. Silverberg, M.D, The George Washington University Medical Center, Washington, D.C. 20037

Philip C. Ursell, M.D., Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Nai-San Wang, M.D., Ph.D., Associate Professor of Pathology, Department of Pathology, McGill University, Montreal, P.Q. H3A 2B4 Canada

Melvin B. Weiss, M.D., Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Gail S. Williams, M.D, Assistant Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, New York, New York 10032

Contents

1

England and King George III's Illness: From Sweeney Todd to Porphyria

Jay H. Lefkowitch, M.D.

Assistant Professor of Pathology
Department of Pathology
College of Physicians and Surgeons
Columbia University, New York, New York

"A gaming, robbing, wrangling, railing nation without principles, genius, character, or allies; the overgrown shadow of what it was."

—Horace Walpole, 1773

IT WAS THE WORST OF TIMES. As the 18th Century gave way to the 19th, a cloud passed over England. The pastoral and halcyon times depicted in the paintings of Reynolds (1723–1792) and Gainsborough (1727–1788) belied the squalor and rank poverty that flourished in England's cities, especially London.[7] What had occurred was the Industrial Revolution. Landmark developments such as Arkwright's water frame (1769), Crompton's mule (1779), and Hargreaves' jenny had changed the face of industry, and of society.

In London, one child born in four survived. Smallpox, typhus, and dysentery were rife, and the refuse of the crowded slums flowed through street trenches. Drink, gambling, and violence became the popular subjects for critical satire for painters such as Hogarth (Fig. 2) and for writers such as Samuel Richardson, author of the highly successful *Pamela*. Perhaps the greatest of all writers for social reform was Charles Dickens (1812–1870), whose novels sought to expose, through uncanny characterizations and settings of situation, the evils at large in England. In *Hard Times* (1854), for example, the industrialization of the city was deftly described:

> It was a town of machinery and tall chimneys, out of which interminable serpents of smoke trailed themselves for ever and ever . . . and where the piston of the steam engine worked monotonously up and down like the head of an elephant in a state of melancholy madness.

And at the helm of this ship that had veered off course was King George III, the man who lost the American colonies.

GEORGE III AND SWEENEY TODD, THE DEMON BARBER OF FLEET STREET

Legends are created in and of their time. The period of George III's reign laid claim to the emergence of two such mythic conceptions which, although seemingly unrelated, are actually interwoven. The first, that George III was "mad," was a legend handed down to recent generations until the 1960s when the work of Dr. Ida Macalpine and Dr. Richard Hunter[5,6] challenged the idea. The second, the legend of "Sweeney Todd, Demon Barber of Fleet Street," even today rivals that of "Jack, the Ripper" in its ability to conjure up nightmarish fantasies.

Fig. 1. In the recent Stephen Sondheim musical, "Sweeney Todd," Mrs. Lovett (Angela Lansbury) and the murderous barber Sweeney Todd (Len Cariou) celebrated the joys of baking human meat pies. Their desperate lives were fostered by the "madness" of George III's reign. Photo courtesy of Martha Swope.

Peter Haining, in his recent investigation into the character, Sweeney Todd,[4] presents the fascinating hypothesis that this murderous barber was created out of the social and political turmoil fostered by the chaotic rule of a "mad" king, George III. Warring political factions, eager to gain advantage during periods of the King's infirmity, may well have encouraged the impression of judicial laxity which allowed the rise in local crime and miscarriage of justice in the late 1700s. Just such a system would not only have abetted the fearless crimes of a Sweeney Todd, but may have caused them directly. As depicted in the recent musical of the same name (Fig. 1), Sweeney Todd was falsely convicted of a crime and was transported from England by a lecherous judge who had designs on Todd's wife. By this action, the corrupt judge created a crazed barber who later returned secretly to London bent on revenge. While working for retribution, he used his trade to financial success: he slit his clients' throats and baked them into meat pies with assistance from an enamored pie-baker, Mrs. Lovett.

Haining presents considerable evidence that Todd actually existed. The tale of "Sweeney Todd" originally appeared as a serialized story in thirty-seven chapters in *The People's Periodical and Family Library* (1846), edited by E. Lloyd, and was probably written by Thomas Peckett Prest. In 1847, it was presented as a highly successful melodrama by George Dibdin Pitt at the Britannia Theatre in High Street, Hoxton. The local geography of the tale is credible enough. Number 186 Fleet Street, the barber's shop as written in the 1846 tale, can still be found next door to St. Dunstan's church, around the corner from which (allegedly) was Mrs. Lovett's pie shop (now Butterworths, the book publishers, in Bell Yard). "The most dastardly criminal of the age," Todd may have been the synthesis of several real or fictional murderers. Haining cites tales of a barber named "Todd" of Fleet Street, the Demon Barber of La Rue de la Harpe, the five women barbers of Drury Lane, and the Scottish cannibal Sawney Bean. In the playbill of the New York Frazee Theatre's 1924 production of "Todd," a (proba-

Fig. 2. Hogarth's engraving, "The Second Stage of Cruelty," depicted crime in a London street in 1751.

bly spurious) reference is even made to a murderous barber in the Newgate prison. The most cogent pieces of evidence that Haining cites for a real Sweeney Todd consist of two items from the Annual Register of 1784 and 1785, entitled "A Barbarous Barber" and "A Cut Throat Barber,"[4] the latter quoted below:

A Cut Throat Barber

> "A horrid murder has been committed in Fleet Street on the person of a young gentleman from the country on a visit to relatives in London. During the course of a walk through the city, he chanced to stop to admire the striking clock of St. Dunstan's Church and there fell into conversation with a man in the clothing of a barber. The two men came to an argument, and of a sudden the barber took from his clothing a razor and slit the throat of the young man, thereafter disappearing into the alleyway of Hen and Chicken Court, and was seen no more."

Famine, pestilence, working class discontent, and political and religious conflicts spawned the anti-Papist Gordon riots in 1780, and in 1795 a bad harvest resulted in food riots all over the kingdom.[2,7] In 1788, King George III went "mad."

THE KING'S ILLNESS

Five major attacks characterized by multisystem complaints occurred during George's lifetime (1738-1820): in 1765, 1788, 1801, 1804, and finally in 1820. The attacks were chronicled in records of attending physicians and survive in the Willis manuscripts in the British Museum, the Queen's Council Papers at Lambeth Palace Library, Sir Henry Halford's daily diary in the Royal Archives at Windsor, and in Sir George Baker's diary.[5] In 1788, when the King went "mad," throwing the government into frenzy for the investiture of the Prince Regent, George's best-known attack was described in Sir George Baker's diary:[2]

> "I found His Majesty sitting up in his bed, his body being bent forward. He complained of a very acute pain in the pit of his stomach, shooting to the back and sides, and making respiration difficult and uneasy. The pain continued all the day, though in a less degree of acuteness towards the evening."

The King, then 50 years old, was diagnosed as having "biliary Concretions in the Gall Duct," but several months later had undergone an "entire alienation of mind."[5] He was told that his disorder had arisen from not changing his stockings when coming home from hunting, so that he had caught rheumatism in the legs which had flown to the stomach.[2] By February 1789, the illness had passed and 12 years were to elapse before the major attack. The illnesses were all similar, ushered in by cold, cough, and malaise, and were characterized by multisystem complaints: abdominal colic with constipation, tachycardia, hoarseness, weakness and stiffness, cramps, paresthesias, dysphagia, visual disturbances, and evidence of cerebral involvement, with agitation, vehemence, emotional lability, delirium, illusions, delusions and hallucinations. Most of the physicians were stymied as to the nature of the illness. A letter from Lord Grenville of November 20, 1788 indicated one of the prevailing opinions:[5]

> "The cause to which they all agree to ascribe it, is the force of a humor which was beginning to show itself in the legs, when the King's imprudence drove it from thence into the bowels; and the medicines which they were then obliged to use for the preservation of his life, have repelled it upon the brain . . . The physicians are now endeavouring . . . to bring it down again into the legs, which nature had originally pointed out as the best mode of discharge."

Other physicians' views were varied: Jones ("nervous fever"), Pargeter ("delirium without fever"), William Heberden, Jr. ("a peculiarity of constitution of which I can give no distinct account"). John Hunter probably had it right (a "systemic affliction"). It was later that medical thought generated the concept that George's illness was psychological, with theories by Isaac Ray in 1855 ("acute mania"), Jelliffe in 1931 ("manic-depressive psychosis") and Guttmacher in 1941 ("in all probability the disorder was purely mental and the clinical reports were falsified, physical symptoms were invented, or, at least, exaggerated further to fool the public").

The Reverend Dr. Francis Willis and sons, physicians "expert" in treating the insane, were called in to treat the King, which they did with

tried-and-true therapeutic regimens: the straight-waistcoat, emetics, purges, and blisters. A restraining chair was fashioned, into which the King was strapped and given "severe lectures" by the good Dr. Willis. A page from the Robert Willis diary, on exhibit in the British Museum, gives an example of the "therapeutic" course:

> "Slept five hours in the night — turbulent and restrained. Good-humored at the time of our visit and more collected, but the whole conversation had reference to his disordered actions. Rather silent all day — slept about twenty minutes in the afternoon and an hour and one half in the evening — went to bed willingly but sillily at nine."

The corresponding bulletin issued to the public read:

> "The King has continued nearly in the same state throughout the week. The antimony was ordered to be continued and the calomel twice a week as before."

THE NATURE OF THE ILLNESS

Over 100 years after George III's death, in 1966, Ida Macalpine and Richard Hunter presented evidence against interpretations of the King's "madness" as insanity or manic-depressive psychosis.[5] The abdominal cramps, signs of disturbed anatomic and vasomotor function, and hysterical personality were all consistent with the diagnosis of acute intermittent porphyria (AIP), as were episodes of "red" or discolored urine. The excess urinary excretion of porphobilinogen (a porphyrin precursor —see Fig. 3) in this disorder is responsible for the urine's characteristic burgundy-wine color on standing in sunlight and for the positive diagnostic test with Ehrlich's aldehyde reagent.[3]

THE INHERITANCE

George III's genetic inheritance stemmed from both the Hanover and Stuart lines. With the death of Princess Anne in 1714, the Stuart reign had ended. Sophia, granddaughter of James I, married Ernest Augustus, Elector of Hanover, and thus introduced the House of Hanover to British monarchy. Their son was George I (Fig. 4). George II succeeded his father in 1727 and died in 1760 following rupture of an aortic aneurysm, having outlived his eldest son Frederick, Prince of Wales, by more than 9 years. George III succeeded to the throne in 1760. While every royal family has its ups and downs, the House of Hanover seemed particularly predisposed to scandal and fierce family battling, especially between George II and Frederick. The best that could be said of the Prince of Wales by his mother, Queen Caroline, was: ". . . the greatest liar, and the greatest canaille, and the greatest beast in the whole world."[2]

Macalpine and Hunter, in researching the Stuart and Hanover lineage, traced evidence of porphyria through 400 years and 13 generations, back to Mary, Queen of Scots (1542-1587). That estimable lady was said to be afflicted with "obstruction of the spleen"[6] and on at least one occasion was suspected of having

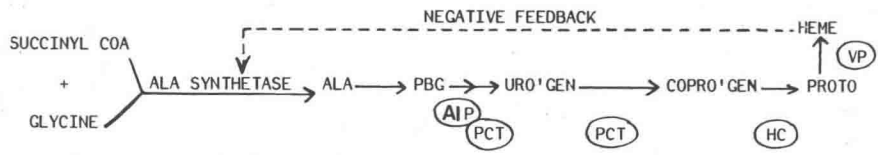

Fig. 3. The porphyrias result from enzyme dificiencies in the biosynthesis of heme. With absent negative feedback by heme, various porphyrin precursors are synthesized to excess and accumulate in tissue. ALA = aminolevulinic acid, PBG = porphobilinogen, uro'gen = uroporphyrinogen, copro'gen = coproporphyrinogen, proto = protoporphyrin. The clinical forms of porphyria are indicated in circles: AIP = acute intermittent porphyria; PCT = porphyria cutanea tarda; HC = hereditary coproporphyria; VP = variegate porphyria.

Fig. 4. Early Hanovers: (*a*) George I; (*b*) George II; (*c*) Frederick, Prince of Wales and his sisters; and (*d*) George III.

been poisoned. The threads of acute intermittent porphyria and variegate porphyria were traced to other members of the line, including James VI of Scotland, Henry Frederick, Prince of Wales, Henrietta Anne, Duchess of Orleans, George IV, and Princess Charlotte Augusta of Wales. In each case, indications of photosensitivity, visceral disorders such as abdominal cramps, autonomic dysfunction, and personalities verging on the "hysterical" could be found, all attributable to deposition of porphyrin precursors characteristic of the disordered heme biosynthetic pathway in the various porphyrias (Fig. 3).[1]

GEORGE III AND HIS ERA: A REAPPRAISAL

George III has come to be known as the "mad" king who "gloried in the name of Britain"[2] and lost the American colonies. He was, pehaps justifiably, labeled a neurotic and unstable character. There is also first-hand evidence, however, from George's own writings, that he was not a monarch without a heart or sense of responsibility. In an apologia written to his son (about 1766) regarding his political conduct, George III wrote:[2]

> "That I have erred is undoubted, otherwise I should not be human, but I flatter myself all unprejudiced persons will be convinced that whenever I have failed it has been from the head, not the heart."

Few realize, however, that he founded the Royal Academy with funds from his private purse, purchased the books in the King's Library of the British Museum as the nucleus of a national library, maintained his own astronomy observatory, and was a patron of many scientific pursuits (he even had Benjamin Franklin's lightning rods installed at Buckingham Palace as soon as they were available). His illness can

now be understood in the context of a biochemical disorder, porphyria, which had been passed down since the time of Mary, Queen of Scots (1542-1587).

Perhaps more remarkable is the insight gained to the entire period of his reign, during which the Industrial Revolution created a discontented working class, "rich" only in poverty, disease, and crime. The fictional creations that arose from that era, such as "Sweeney Todd," on face value represent their authors' imaginative renderings of the multifaceted nature of the times. They command a greater perspective when evaluated in terms of the currents of political, social and economic thought that surrounded them and in the light of more recent medical evidence that has allowed us a better understanding of King George III.

References

1. Bloomer, J.R.: The hepatic porphyrias. Pathogenesis, manifestations, and management. *Gastroenterology* **71**: 689-701, 1976.
2. Brook, J.: *King George III.* Panther Books Ltd., Herts, England, 1974.
3. Goldberg, A. and McColl, K.E.L: The porphyrias. *Medicine (London)* **11**: 551-555, 1979.
4. Haining, P.: *The Mystery and Horrible Murders of Sweeney Todd, the Demon Barber of Fleet Street.* Frederick Muller Limited, London, 1979.
5. Macalpine, I. and Hunter, R.: The "insanity" of King George III: A classic case of porphyria. In *Porphyria —A Royal Malady.* Articles published in or commissioned by the British Medical Journal. British Medical Association, London, 1968, pp. 1-16.
6. Macalpine, I. and Hunter R.: Porphyria in the royal houses of Stuart, Hanover and Prussia: A follow-up study of George III's illness. In *Porphyria — A Royal Malady.* Articles published in or commissioned by the British Medical Journal. British Medical Association, London, 1968, pp. 17-57.
7. Plumb, J.H.: *England in the Eighteenth Century.* Penguin Books, New York, 1963.

2

Staging, Typing, and Grading of Colorectal Cancer: A Critical Review of Current Classification Systems*

Wolfgang Remmele, M.D.

Institut für Pathologie der Städtischen Kliniken
Wiesbaden, Federal Republic of Germany

INCIDENCE OF COLORECTAL cancer is steadily increasing in most Western industrial countries including the United States and the Federal Republic of Germany.[72,77,81] Therefore, biopsies and operation specimens of this tumor belong to the material most frequently delivered to the pathologist for further examination.

The endoscopist and the surgeon expect not only a simple description of the pathological findings but an interpretation that may be translated into terms of prognostic significance. Consequently, the precise classification of the tumor is part of each pathological examination of colorectal cancer. It consists of tumor staging (i.e., estimation of tumor extension), tumor typing (i.e., definition of its histological type), and tumor grading (i.e., description of its cytological and/or histological grade of differentiation).

During the last decades, several systems for the classification of colorectal cancer have been developed. Some of these systems represent modifications of systems previously described by other authors. It is not a rare event, however, when an original definition is quoted incorrectly in subsequent papers. Thus the results of different authors concerning the incidence of stages, types, and grades, or of the 5-year survival rate in different stages and grades, cannot be compared unless the method which has been used in order to classify the cases has been verified. Otherwise, findings which are not comparable are correlated.

The present paper presents a review of the most common classifications for colorectal cancer. An attempt is made to analyze each system in regard to its pros and cons and to eliminate false interpretations from further use. Some introductory remarks will deal with the basic requirements and the anatomical base of colorectal cancer staging. A schedule for the classification of colorectal cancer specimens in daily pathological practice will be proposed.

* Abbreviations used in this paper are: AJC = American Joint Committee for Cancer Staging and End-Results Reporting; UICC = International Union Against Cancer; and WHO = World Health Organization.

BASIC REQUIREMENTS FOR PATHOLOGICAL TUMOR CLASSIFICATIONS

It is the purpose of each morphological tumor classification to correlate the pathological findings with the patient's probable prognosis. Therefore it has to be based upon sufficient data from *long-term (at least 5 years) studies on a large number of patients using reproducible and unobjectionable methods.* The definition of certain tumor stages and grades is valuable only if prognosis varies considerably from one stage or grade to the others.

Moreover, a useful classification system requires *that the examination of the tissue specimens always follow the same standardized schedule* and *that it can easily be performed at any time and by any pathologist* under the circumstances of daily routine work. In other words, it must be as extensive as necessary, but as easy and limited as possible. It must contain all relevant data, but it should not be burdened with unnecessary work.

Finally, the *code* by which the morphologic findings are expressed, should be easily understood. Therefore, *few symbols* should be used, and the subdivision of stages and grades should not go too far. *The code should identify the method* by which the tumor has been classified. In the AJC classification of colorectal cancer, this requirement is met by the introduction of different prefixes. pTNM means "postsurgical treatment — pathologic staging," cTNM "clinical-diagnostic staging," sTNM "surgical — evaluative staging," rTNM "retreatment staging," and aTNM "autopsy staging." pTNM has been adopted by the UICC classification of 1979. Dukes' classification does not require a prefix since it is a pathological classification by definition.

ANATOMICAL BASIS OF COLORECTAL CANCER STAGING

The spread of cancer within the bowel wall depends largely upon the anatomical structure of the latter. The occurrence of lymphatics within the different layers and the course of the large lymphatics outside the wall to the regional lymph nodes are of special importance.

The *smallest lymphatic capillaries are found in the mucosa immediately above the muscularis mucosae.* Normal, hyperplastic, and adenomatous colonic mucosa contain a lymphatic plexus associated with the muscularis mucosae; only some blind loops extend upwards for a short distance into the lamina propria but not beyond the level of the base of the crypts.[51] They explain why the so-called adenoma with severe cellular atypia (WHO classification from 1976) may metastasize in rare cases (personal observation).[51] Formerly it had been claimed that the mucosa of the cecum would not contain any lymphatic capillaries.[126]

With regard to these anatomic findings, it may be expected that very early types of colorectal cancer, only superficially invading the lamina propia, will not metastasize. Also it may be expected that the risk of tumor spread will increase markedly in cancer extending into the muscularis mucosae. So far, no statistical data are available concerning the prognosis (5-year survival rate) in patients with noninvasive carcinoma *in situ* or invasion only of the superficial mucosa on one hand and in patients with carcinoma invading the deeper layers of the mucosa and the muscularis mucosae on the other. An exceedingly low risk of cancer with only superficial involvement of the bowel wall is not supported by the findings of Wood et al.[167] for prognosis in T_{IS} N_0 M_0 and T_1 N_0 M_0 cases (75 and 82% 5-year survival rate, respectively), but it must be realized that the T_{IS} cases of this series lack a precise description and that the high mortality figure might have been related to causes other than "carcinoma *in situ.*" Presumably, a number of these cases may have had coexistent ulcerative colitis.[166] The data reported by Cass et al.;[27] (no local recurrence in cases with carcinoma *in situ* and with invasion of the bowel wall not deeper than to the submucosa) is evidence for the good prognosis of patients with only superficial infiltration of the bowel wall.

Lymphatic vessels of small and medium size are present both in the *submucosa and muscularis propria,* the larger vessels being located

within the pericolic-perirectal adipose tissue. Cancer cell thrombi are seen much more often in the medium-sized and large lymphatics than in the small lymphatic vessels of the mucosa and submucosa. This finding is in keeping with the fact that prognosis decreases sharply following invasion of the deeper layers of the bowel wall (Tables V-VIII).

The *muscularis propria* is a natural barrier against the transmural spread of the cancer.[69] If it is penetrated by the tumor, prognosis becomes much poorer. Therefore, it is reasonable to distinguish between cases with and without penetration of the muscularis propria, as in Dukes' classification (stages A and B) or in the modified AJC classification of December 1979, although only for the rectum (stages Ib and II[166]).

If the tumor involves the *serosal surface* it bears the risk of peritoneal implantation, and prognosis worsens again.[42,47,163] In Turnbull's modification of the Dukes' system, this point is marked by the transition from stage B to stage D, and in the AJC and UICC classifications by the transition from stage IB to stage II. In the rectum, which lacks a peritoneal cover, peritoneal seeding corresponds to tumor extension beyond the muscularis propria (AJC and UICC) and to adjacent organs (Turnbull), respectively.

The *lymph flow from the colon and rectum to the regional lymph nodes* has been thoroughly studied and summarized by several authors.[31,55,61,62,65,67-69,76]

The *lymph flow from the colonic wall* traverses the epicolic and paracolic lymph nodes and reaches the intermediate lymph nodes following the course of the major vessels supplying the colon.[31,65,87] These lymph nodes are called "distal lymph nodes" and correspond to the "regional lymph nodes" of the UICC and AJC classification (N1). The para-aortic lymph nodes ("principal lymph nodes"[65,100] and "central lymph nodes"[76]) are the next station. Together with "other subdiaphragmatic intra-abdominal lymph nodes" they are summarized under the heading of "juxta-regional lymph nodes" (N_4) by the UICC classification. In the AJC classification, cases with para-aortic lymph nodes metastases are called M_1 instead of N_4.

The *proximal (intraperitoneal) part of the rectum* is drained by lymphatics and lymph nodes along the superior hemorrhoidal vessels. The lymph from the *distal (extraperitoneal) rectum* follows the same main route,[55,65] but it may also be drained laterally[4] into lymph nodes along the internal iliac vessels or distally into lymph nodes at the posterior face of the rectum.[65] Inguinal lymph node metastases are observed only after the cancer has invaded the skin of the anus or the perianal region.[65]

Sometimes the flow of lymph bypasses epi- and paracolic lymph nodes or even the intermediate lymph nodes, flowing directly to the para-aortic nodes,[55,65] either due to abnormal course of the lymphatics[55] or because of destruction of lymph nodes by inflammation, trauma, surgical intervention, or irradiation.[31]

Prognosis worsens progressively with increasing spread of the cancer within the lymphatic system. Therefore each classification system separates the cases with only distal lymph node involvement from those with proximal metastases (Dukes: C_1 vs. C_2; UICC: N_1 vs. N_4; AJC: N_1 vs. M_1). If C_2 metastases are present, even high ligations of the inferior mesenteric artery at the level of the aorta with removal of the lymph nodes lying above the origin of the left colic artery does not improve the overall survival rate in patients with cancer of the descending and sigmoid colon and rectum.[70]

Retrograde and atypical spread of tumor cells markedly worsens the patient's prognosis. Usually it is observed in far-advanced cases of colorectal cancer. In Grinnell's series of 34 cases[71] an average of 16 lymph node metastases per specimen was found.

Extramural retrograde spread was found in 5/63 *rectal tumors* (7.9%) by Grinnell.[68] In 1966,[71] the same author described 11 cases among a total of 309 rectal cancers (3.6%). In five cases (1.7%), the tumor had spread downward to lymph nodes 1.5-5 cm below the primary growth. In six more cases, metastases were found in lymph nodes along the middle hemorrhoidal artery. Distal or lateral spread was the result of lymphatic block from metastases in the chain of lymph nodes normally draining the rectum in each case. Gilchrist and

David[62] observed lymph node metastases from 1 to 5 cm below the tumor in 4.6% of rectal cancers localized below the promontory of the sacrum. Prior to the careful studies by Gilchrist and David[61,62] and Grinnell,[67-69,71] who both used the clearing technique and examined several thousands of lymph nodes, few cases of retrograde spread had been described.

In the *colon, extramural lateral spread* into paracolic lymph nodes on either side of tumors located in various segments of the colon and rectosigmoid was observed in 7% (16% of cases with metastases) with a maximum spread of 13 cm.[68] In 1966,[71] Grinnell reported an incidence of only 1.5% (nine cases among a total of 604 carcinomas of the colon) with distances between 5 and 37 cm (average: 12 cm) in the fixed specimen. In three more cases, metastases were found in the gastroepiploic nodes along the greater curvature of the stomach.[71] In all 12 cases, lymphatic block was caused by lymph node metastases near the origin of, or along the course of, the ileocolic, middle colic, or inferior mesenteric arteries. The block caused shunting of the lymph flow into more circuitous routes.[67,68] In only a few of Grinnell's previous cases could the lateral spread not be explained by lymphatic block, unless the blocking nodes lay outside the excised specimen.[68]

Intramural spread of cancer cells in lymphatics and tissue spaces of the *long axis* of the rectum and rectosigmoid may exceed 5 cm beyond the macroscopically visible border of the lesion, provided that the bowel wall is examined in serial sections.[28] Retrograde intramural spread up to 4 cm in curative cases and up to 7 cm in cases with only palliative resection was described by Grinnell.[71] The incidence was 11/93 cases of cancer of the rectum and rectosigmoid (11.8%). Lower values (up to 1.2 cm) were reported by Black and Waugh[11] in cancer of the descending colon (average: 0.242 cm), sigmoid (average: 0.19 cm) and rectosigmoid (average: 0.135 cm). In rectal cancer, invasion of nerves was seen as far as 10 cm from the site of the primary growth.[135]

The studies on intra- and extramural spread of colorectal cancer are of utmost importance for surgery. They indicate that wide resection of the bowel and mesentery, especially in the transverse and left colon, essentially determine the prognosis.[47] On the other hand, unnecessarily radical procedures should be avoided, e.g., in cancer of the rectosigmoid.[71] Lymph nodes should be removed at the highest possible level since metastases are found in the C_2 node of Dukes in 12-13.8% of rectal cancer cases[38,68] and in 16% of cases with cancer of the colon.[68]

REVIEW OF THE MOST COMMON STAGING SYSTEMS FOR COLORECTAL CANCER

Introduction

Dukes' classification[35,55] is the most widely used among the common classifications for colorectal cancer. A first attempt published in 1929[34] was replaced 3 years later[35] by the introduction of three stages (A, B, C) and modified in 1935 by the subdivision of C into C_1 and C_2.[55] Dukes' system has been modified by many authors. The best known modifications were published by Kirklin et al.,[92] Astler and Coller,[3] and Turnbull et al.[152]

Recently, two other classifications have been described: the TNM system developed by the UICC (at present in its third edition from 1979)[153] and the TNM system of the AJC[100] (reprinted in 1978 and modified in December 1979).[166] These systems and other less familiar classifications will now be described and compared in regard to their practical value (for summary see Table I). The definitions of stages will be fully quoted since they are frequently reported incorrectly.

Dukes' Classification[35,55]

In a 1929 paper,[34] Dukes described the following preliminary classification of carcinoma of the rectum:

> "*A cases* are malignant tumours in which the growth extends into the submucosa, but not into the muscle coat. *B cases* are malignant tumours in which the growth extends into the muscle coat, but has not yet spread by direct