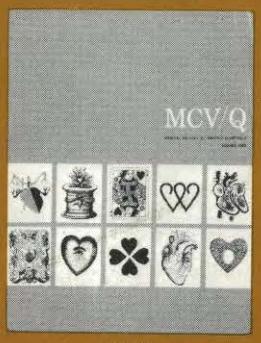
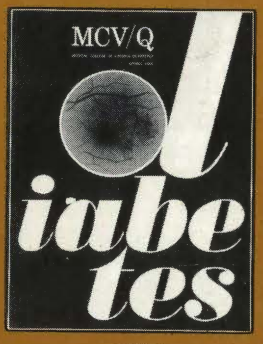
MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
VOLUME SIXTEEN • NUMBERS THREE & FOUR • 1981

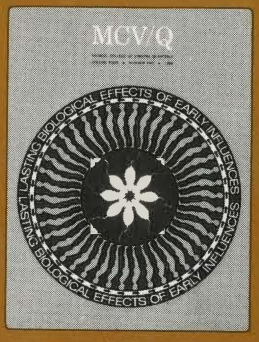


1965

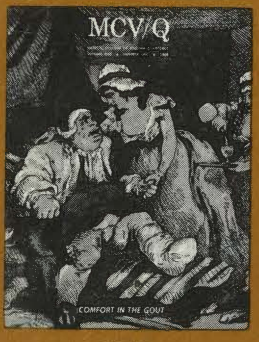


1966

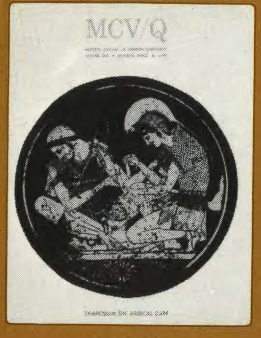
1967



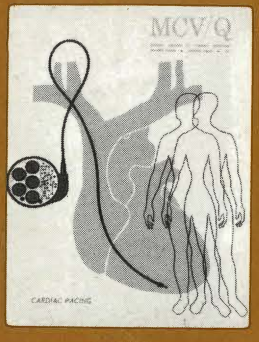
1968



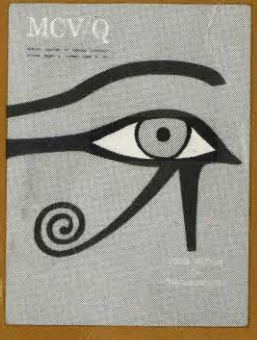
1969



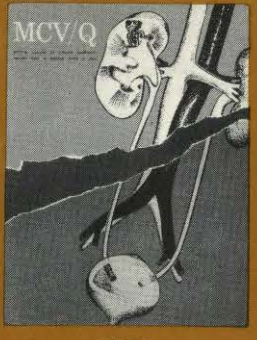
1970



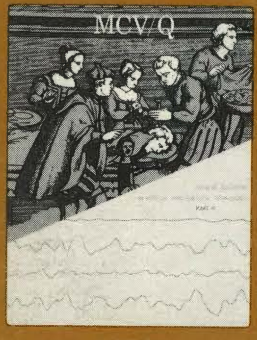
1971



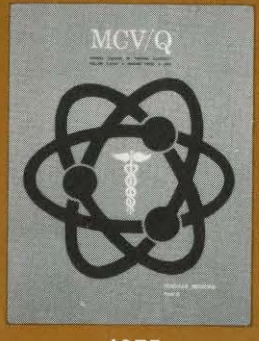
1972



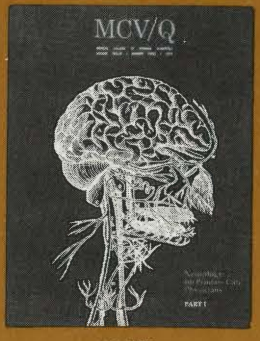
1973



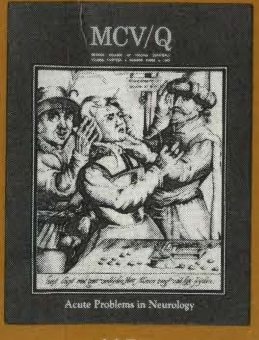
1974



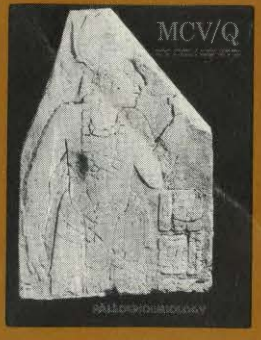
1975



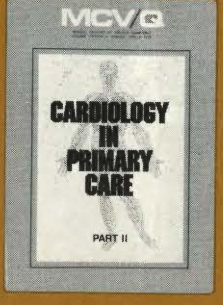
1976



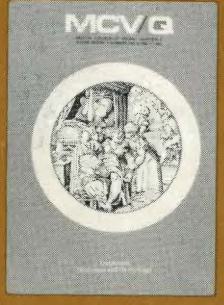
1977



1978



1979



1980

MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY

A Scientific Publication of the School of Medicine
Health Sciences Division of Virginia Commonwealth University

1981 • Volume Sixteen • Numbers Three and Four

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
Published quarterly (Spring, Summer, Fall, Winter) by the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University. The QUARTERLY publishes articles of original research and review in basic and clinical sciences. Contributions from outside the Medical College of Virginia faculty are invited. *Correspondence:* MEDICAL COLLEGE OF VIRGINIA QUARTERLY, Box 26, Medical College of Virginia, Richmond, Virginia 23298. Phone (804) 786-0460. *Third class postage paid at Richmond, Virginia.*

EDITORIAL ADVISORY BOARD
L. GREGG HALLORAN
HUNTER H. MCGUIRE
J. CRAIG MCLEAN
KINLOCH NELSON
JOHN R. TAYLOR

EDITORIAL CONSULTANTS
LARRY F. CAVAZOS *Boston*
FAIRFIELD GOODALE, JR. *Augusta*
RICHARD G. LESTER *Houston*
SAMI I. SAID *Dallas*
MALCOLM E. TURNER, JR. *Birmingham*

EDITOR
FREDERICK J. SPENCER

EDITORIAL ASSISTANT
ANNE L. M. BOWMAN

COVER DESIGNER
RAYMOND GEARY

ISSN 0025-7141
© 1981 by the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University.
Printed by The Byrd Press, Richmond, Virginia

The MCV Quarterly *ceases publication with this issue. No journal of this type can be self-supporting and we bow to the inevitable reality of inflation.*

The idea of the Quarterly *came from Sami Said. Almost single handed he cajoled and coerced the Dean of the School of Medicine into finding the money for publication. Throughout its existence* MCV/Q *has remained true to its stated purpose of disseminating "scientific information from all sources", resisting several attempts to convert it into a "house journal" or popular newssheet. In essence, it has been the printed pivot of continuing education in the medical school.*

It is hard to name the people behind the success, albeit temporary, of MCV/Q. *The editors, of course—Sami Said and Fair Goodale—but even more so the Managing Editors—the last of whom was Mary Park Johnson; the cover designer—Raymond Geary—whose eye catching, balanced designs have been a feature of the* Quarterly *since its inception; and finally, the Deans of the School of Medicine—Drs. Kinloch Nelson, Warren Pierse, and Jesse Steinfeld.*

"Publish or perish" is an academic aphorism today. Regretfully, we perish—but at least we published for sixteen enjoyable years.

FJS

THE MEDICAL COLLEGE OF VIRGINIA SCHOOL OF MEDICINE

Continuing Education Programs for 1982

DERMATOLOGY AND INTERNAL MEDICINE

Date: February 12–14, 1982
Location: The Homestead, Hot Springs, Virginia
Tuition and Fees: $220.000

A first time presentation providing the dermatologist and the internist with current concepts in diagnosis and management of skin disorders with systemic manifestations and systemic diseases involving the skin. The format includes lecture, discussion, and workshops.

PEDIATRIC RADIOLOGY

Date: February 28–March 4, 1982
Location: The Williamsburg Lodge, Williamsburg, Virginia
Tuition and Fees: $330.00

Radiologists and other treating pediatric diseases are presented with the newer techniques available in diagnosis. Some of the topics include Ultrasound, UTI, Pneumonia, Generalized Orthopedic Diseases and Lesions of the Lungs.

RETINAL DISEASES AND OCULAR TUMORS

Date: March 19–21, 1982
Location: The Williamsburg Lodge, Williamsburg, Virginia
Tuition and Fees: $250.00

An in-depth exploration of the clinical diagnosis and management of retinal disease and ocular tumors. Practicing ophthalmologists are invited to hear lectures, participate in small group sessions, and bring difficult cases for consultation with MCV and guest faculty.

CLINICAL CONCERNS IN PRIMARY CARE

Date: April 16–18, 1982
Location: The Hospitality House, Williamsburg, Virginia
Tuition and Fees: $225.00

Primary care physicians are involved in workshops planned around three major areas of concern: hematology, infectious disease, and oncology. Topics include: anemias, work-up and management of the bleeding patient, upper respiratory infections, abuse of antibiotics, treatable cancers and early diagnosis, and management of common cancers.

SPRINGFEST: A CME PROGRAM IN PEDIATRICS

Date: April 22–24, 1982
Location: The Hospitality House, Williamsburg, Virginia
Tuition and Fees: To be announced

Behavioral aspects, dermatology, office emergencies, and other selected topics are explored for new clinical information, implications, issues, and answers. Pediatricians share in lectures, discussions, and small group sessions.

EMERGENCY MEDICINE

Date: April 23–25, 1982
Location: Quality Inn—Fort Magruder, Williamsburg, Virginia
Tuition and Fees: $195.00

Lectures and workshops designed to provide emergency room and office based physicians with practical clinical approaches to basic medical and surgical emergencies. Some of the topics are sprains/strains, common anorectal problems, cardiac drugs, arrhythmias, splinting, and suture techniques.

HANS BERGER DAY: EEG SYMPOSIUM

Date: May 17–18, 1982
Location: Baruch Auditorium, Richmond, Virginia
Tuition and Fees: To be announced

Designed for physicians and other health professionals who use EEG as a diagnostic tool. Topics include intractable seizures, cerebral death, stroke, and degenerative diseases of the brain.

RECENT TRENDS IN CLINICAL RADIATION ONCOLOGY

Date: May 20–22, 1982
Location: The Hospitality House, Williamsburg, Virginia
Tuition and Fees: $250.00

For physicians involved in the management of cancer. Lectures and small group sessions address childhood cancer, Hodgkins Disease, Non-Hodgkin Lymphoma, prostate, cervix, ovarian, paranasal, recto-sigmoid, breast, larnyx, and testicular carcinoma.

GYNECOLOGIC UROLOGY AND PELVIC SURGERY

Date: May 29–31, 1982
Location: The Homestead, Hot Springs, Virginia
Tuition and Fees: To be announced

Reviews basic and advanced concepts in gynecologic urology and pelvic surgery. Formal presentations and small group sessions allow for didactic and direct exchange of information.

CARDIOLOGY

Date: June 18–20, 1982
Location: The Hospitality House, Williamsburg, Virginia
Tuition and Fees: $230.00

For those who practice cardiology. Small group sessions highlight important information: deciding about valvular heart surgery, hypertrophic myopathies, drug management of ventricular arrhythmias, intervention with acute myocardial infarct, and recent advances in treating heart failure.

PEDIATRICS AT THE BEACH

Date: August 4–7, 1982
Location: Sheration Beach Inn, Virginia Beach, Virginia
Tuition and Fees: $235.00

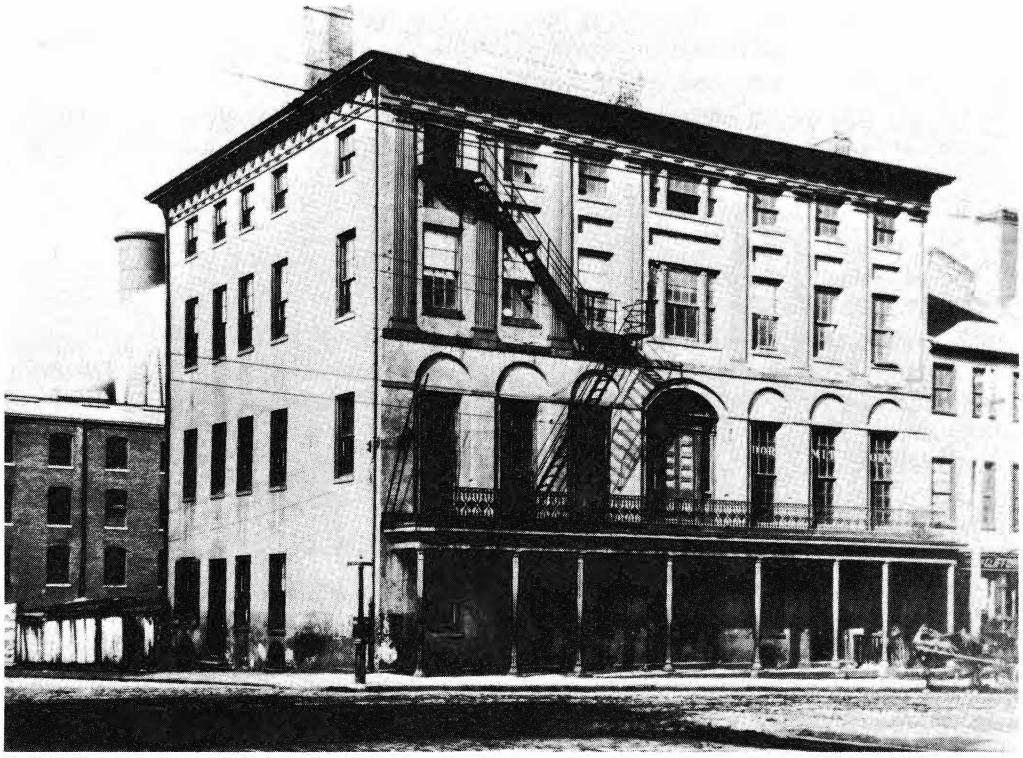
Allergy, immunology, dermatology, and orthopedics for the practicing pediatrician. Lectures and small group sessions designed to provide clinical insight into topics such as persistent urticaria, steroids and asthma, fungal dermatoses, and common orthopedic problems.

SUMMER RETREAT: PRACTICAL ISSUES IN PRIMARY CARE

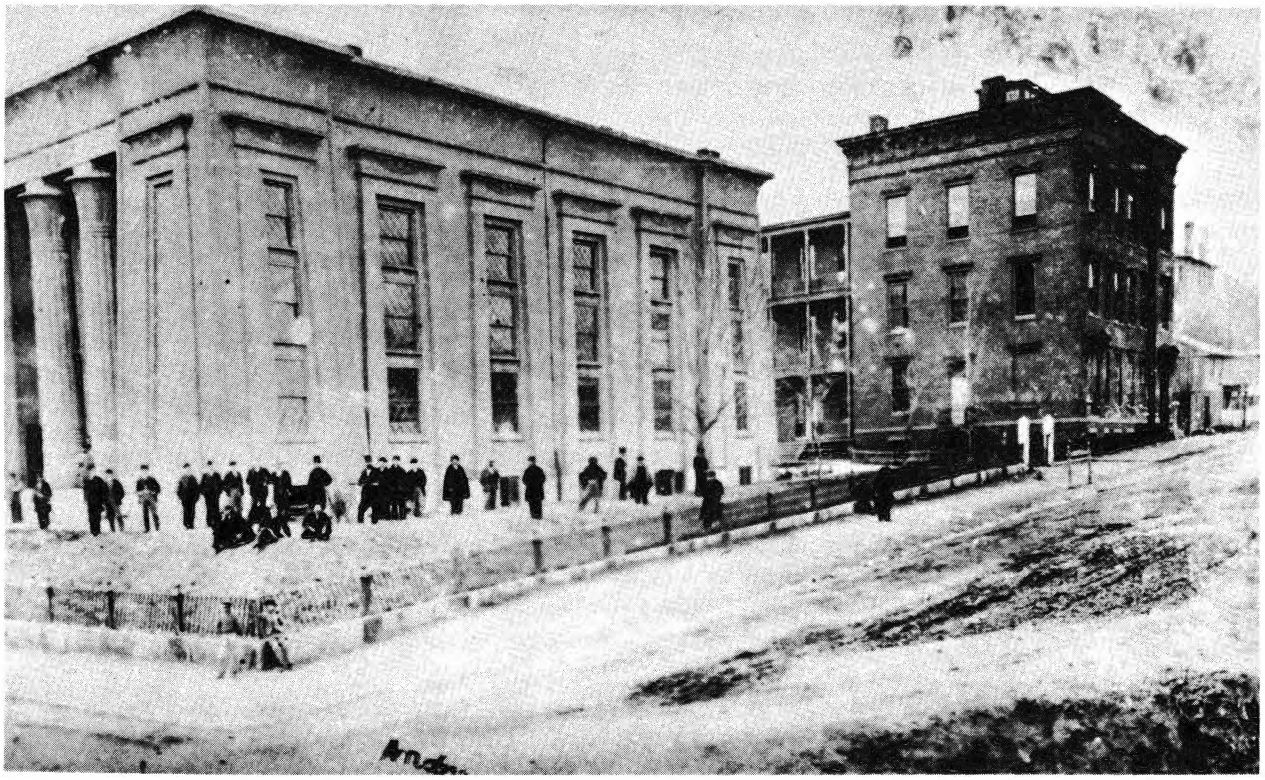
Date: August 11–14, 1982
Location: Sheraton Beach Inn, Virginia Beach, Virginia
Tuition and Fees: $235.00

For the family physician, the general practitioner, the physician delivering primary care. Lectures and discussion providing doctors with opportunities to discuss issues in cardiology, management of pain, antibiotics in medicine and surgery, and medical malpractice.

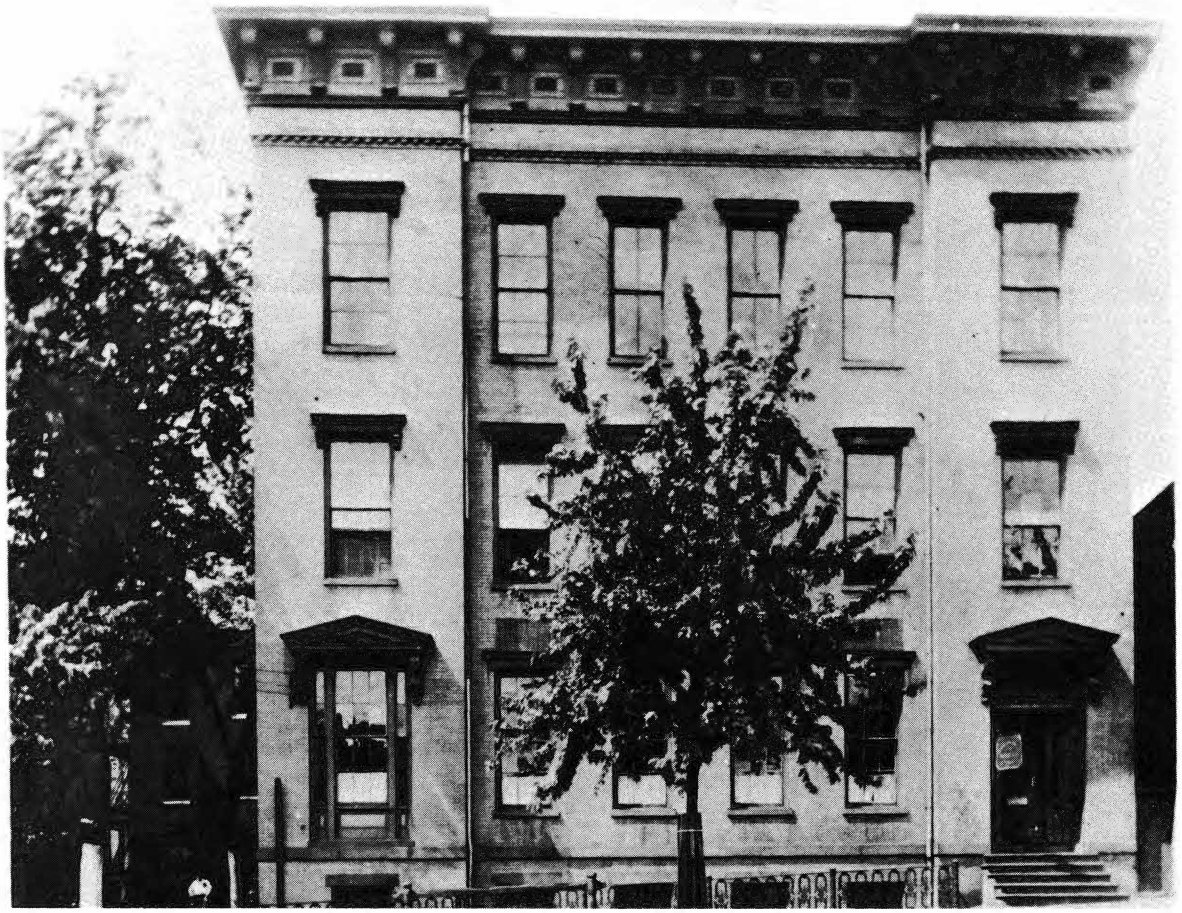
The Medical College of Virginia (MCV) is the State's major provider of continuing medical education conferences and institutes. Two thousand physicians from across the United States participated in MCV programs during 1980–81. Nationally known MCV faculty and distinguished guest faculty share medical insights on the most recent and successful diagnostic and therapeutic techniques. Participants are encouraged to share problem cases. Leisurely surroundings, informed practitioners, and involved faculty blend effectively to create pleasant and meaningful experiences in continued learning.



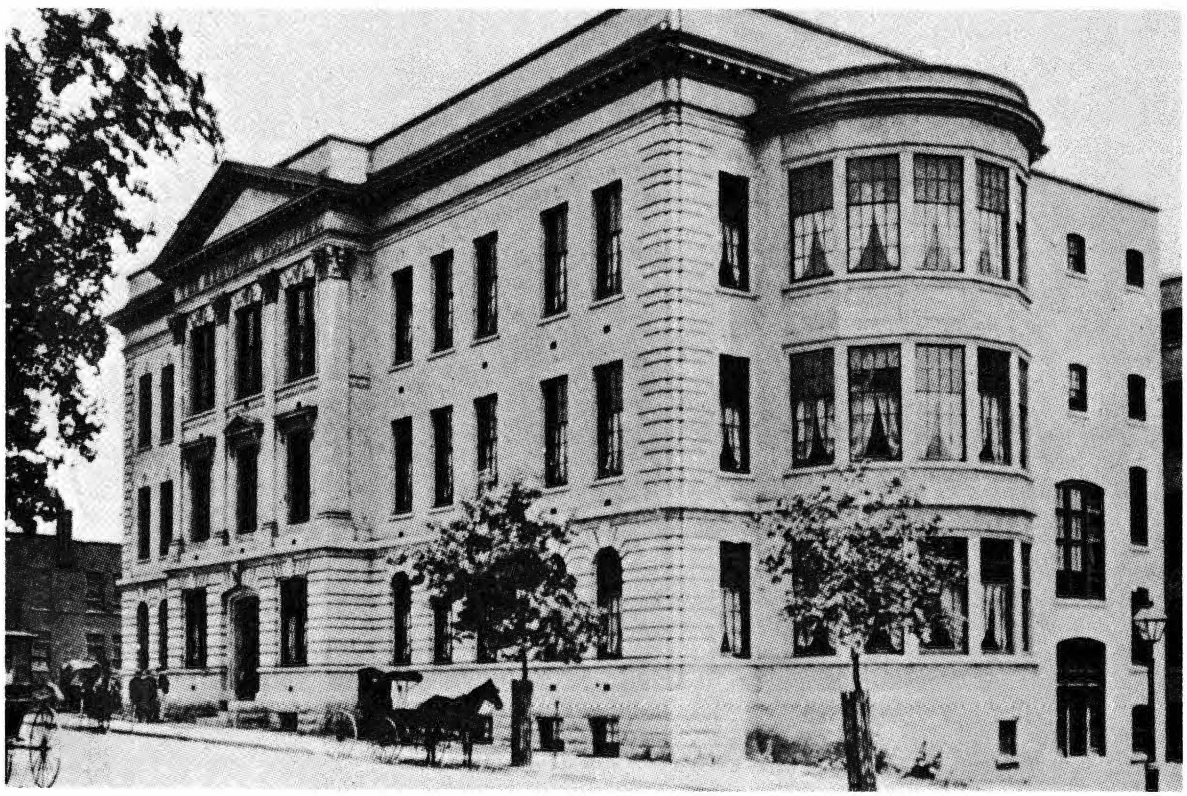
UNION HOTEL, 19th and Main Streets—1838



Egyptian Building—1845

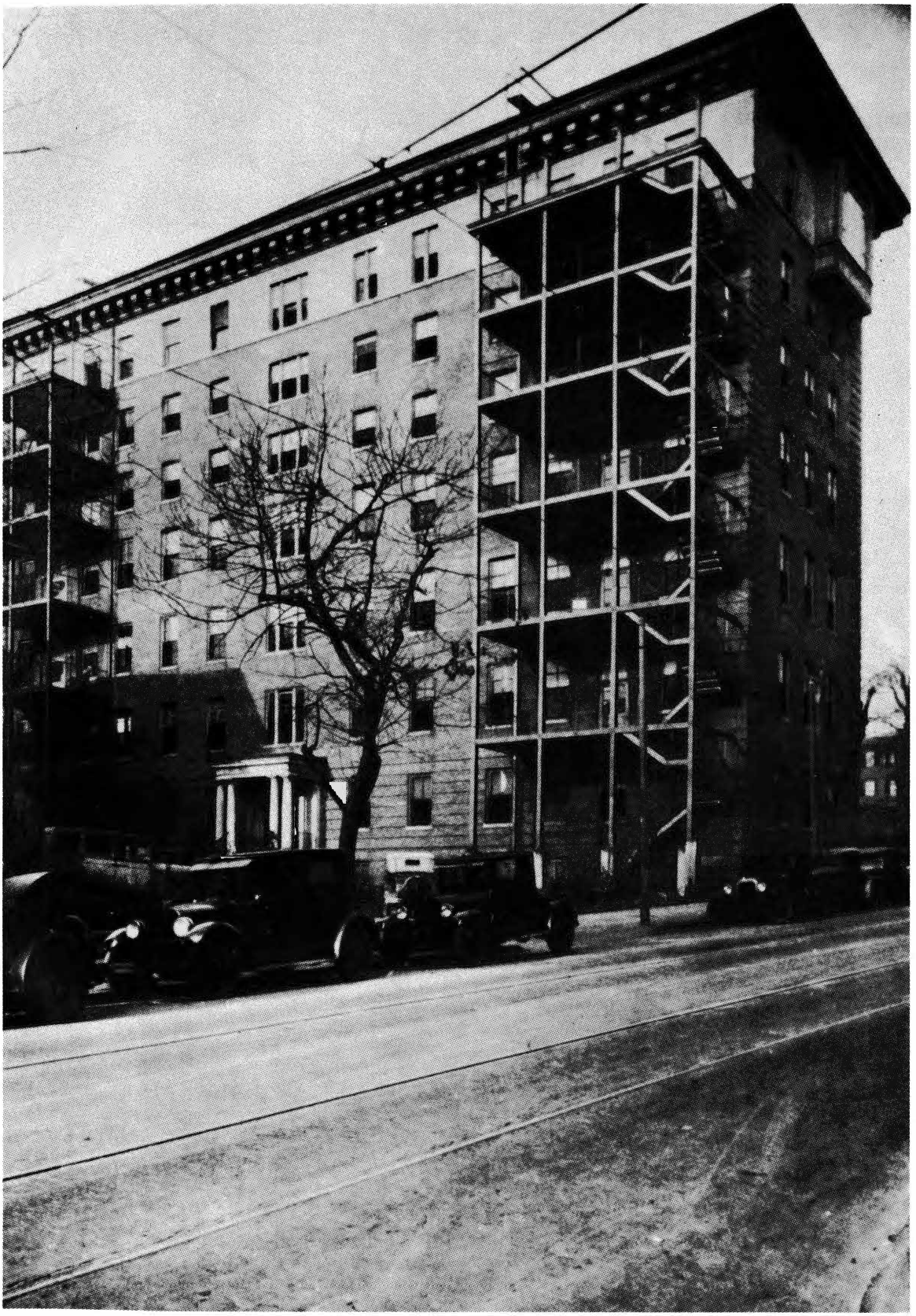


Old Dominion Hospital—1861



Memorial Hospital (MCV South)—1903

Dooley Hospital—1920



St. Philip Hospital (MCV East)—1920

A. D. Williams Memorial Clinic—1928

The Gay Nineties: Oscar Wilde Reconsidered

FREDERICK J. SPENCER, MD

Professor and Chairman, Department of Preventive Medicine, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Sex and hypocrisy have always been bedmates, but never more than in Victorian England. In the "Gay Nineties" promiscuity was widely accepted in all social classes, although the aristocracy hid its lust behind a strict code of propriety. Country house parties catered to infidelities with the approval of the Prince of Wales, himself a notorious womanizer.

The sexual athleticism of His Royal Highness, Albert Edward, has been covered in innumerable books.[1] Protected from women by the vigilance of his mother until he was 20 years old, he was introduced to the delights of the bed in Ireland by an actress/camp follower of the Grenadier Guards. The bevy of mistresses that followed resulted in one court case and several minor scandals. His future queen, Alexandria, withstood his dalliances with dignity, finally sending for Mrs Alice Keppel, his last and firmest mistress, when he was on his death bed, remarking at the same time that "He always loved me the best."

In 1890, the word "gay" was used for heterosexual relationships with prostitutes, today's use not coming into effect until the 1930s, and only into common use in the past ten to 15 years.[2] The "Gay Lothario" of 1703 was certainly no homosexual.[3] So the "Gay Nineties" were very gay indeed, in the old-fashioned sense of the word. As Mrs Patrick Campbell is supposed to have said, "You can do what you like as long as you don't frighten the horses." But sodomy was another matter. This most despicable crime of all—the "abominable crime of buggery"—was the indictment brought against Oscar Wilde in 1895.[4]

Oscar Fingal O'Flahertie Wills Wilde was born in Dublin, Ireland on 16 October 1854. His father, Sir William Wilde, the son of a doctor, was a pioneer otorhinolaryngologist and opthalmologist, a combination of specialties which existed well into the twentieth century. Among Sir William's innovations were angled nasal forceps and "Wilde's Incision," a deep opening of the mastoid air cells in the treatment of acute mastoiditis.[5] He was also a noted Irish antiquary and archaeologist. Unprofessionally, his sexual promiscuity led to several illegitimate children and to a prosecution for molesting a female patient of dubious virtue; she was awarded ¼ d in damages—the smallest possible sum!

Oscar Wilde's mother, known as Speranza, was an accomplished poet and the author of several revolutionary pamphlets, a sufficient reason for her nom-de-plume, even if women authors had been socially acceptable in the 1850s.[6] Oscar was the second of Lady Wilde's children, and his elder brother, William, later known as "Wuffalo Will," became a notorious and intemperate man-about-town.[7] It is said that Oscar's mother wanted a daughter and showed her disappointment by dressing him in girl's clothes until the birth of her third child, a daughter, Isola, when Oscar was three years old.[8] Much has been made of a picture of Wilde in a girl's dress at the age of two, the inference being that it was a conditioning factor in his homosexuality, but it is doubtful if it played a significant part in his sexual development as this mode of dressing boys was not uncommon in Victorian Ireland.[9]

After preliminary schooling, Oscar Wilde went to Trinity College, Dublin and thence to Oxford where he acquired two things: a first-class degree—and syphilis from a local harlot by the name of "Old Jess." The resultant mercury therapy left him with blackened, carious teeth for the rest of his life. From Oxford he went to London, where his flamboyant dress and brilliant conversation brought him notoriety, soon enhanced by a more solid reputation as an author of plays, prose, and poetry.

In January 1882, Wilde came to North America, landing in New York where he was besieged by a curious public and press. When asked by customs officials if he had anything to declare, he said, "Only my genius." He reached Richmond on 11 July, notice of his lecture appearing for the first time in the *Richmond Whig* on 28 June 1882, and announcing that tickets priced at $1.00 for seats in the dress circle and front stalls and 50¢ elsewhere were available from Ramos and Moses.

The report of the lecture in the *Daily Dispatch* of 12 July 1882, under the headline, "HOW THE GREAT APOSTLE OF AESTHETICISM LOOKED," is devoted more to Wilde's dress than to his words: "Mr Wilde was dressed in the oft-described silk small clothes, including knee-breeches, &t., silk velvet surtout, old style, satin-lined. There was pending from his neck a long array of white dimity corrugated into numerous ruffles and extending some distance down the diaphragm. Mr. Wilde's appearance was greeted with slight applause . . . . His hair, which was of brown texture, was parted in the middle and worn in ringlets over ample shoulders suggesting Buffalo Bill, only the aesthete is by no means so comely a specimen of manhood as the great Indian scout and prairie warrior."

The critic continued by noting, "An allusion to beautiful women and their influence was recognized . . . as having a personal application to that section of the fair sex present, and was received with vociferous acclaim."

On his return to England, Wilde continued his career as a brilliant writer and critic, meeting the cream of aristocratic London, including James McNeill Whistler, the American expatriate painter.[10] Whistler's reputation as a conversationalist equaled Wilde's, and they became great friends. Wilde, however, extended his criticism to art, and this enraged Whistler who, with some justification, considered that Wilde's knowledge of painting did not qualify him as an art critic. Their open hostility led to the famous story of how Wilde, on hearing Whistler make some particularly witty remark, said, "Jimmy, I wish I'd said that." Whistler replied, "You will, Oscar, you will."

The Gay 90s

In 1891, Oscar Wilde, at the height of his career, met Lord Alfred Douglas, son of the Eighth Marquess of Queensberry. The Marquess, familiarly known as "Q," is best known for the Marquess of Queensberry's Rules, which brought some decorum into the prize ring of the day and remain the basis of modern boxing refereeing.[11] Oscar and Lord Alfred, or "Bosie" as he was known, soon became close friends to the disgust of "Q," who was better known as a bullying sportsman than as a doting father. The Queensberrys were notorious for their sexual escapades, particularly "Old Q," the Fourth Marquess, who, in his eighties, erected a bow window in Piccadilly so that he could ogle passing girls.

This family failing, however, did not lead to "Q's" accepting Wilde's advances to Lord Alfred, and the Marquess, with one of his prize fighters, went to Wilde's house to order him to leave his son alone. After some angry words, Wilde showed "Q" to the door, telling his servant that he was never to admit this "most infamous brute in London" to his house again. Queensberry, in a frenzy, planned to ruin the first night of Wilde's play, *The Importance of Being Earnest*, but was prevented from entering the theatre by a cordon of police, thoughtfully recruited by Wilde.

Frustrated, "Q" stormed into the Albermarle Club and gave his card to the hall porter with instructions that it be handed to Wilde when he next came in; on the back of the card was written, "For Oscar Wilde posing as somdomite." The usual explanation of the incorrect spelling is that the enraged "Q" misspelt "sodomite," but perhaps spelling was not his strong point. Wilde received the card about two weeks later and unwisely sued the Marquess of Queensberry for criminal libel.

The trial attracted the greatest legal minds of the day, and by brutal cross examination, "Q's" counsel showed that the libelous statement was almost certainly true. Wilde's defend-

ing counsel declared his intention to withdraw from the case, first in private to Wilde, and the next day in court. The Marquess was immediately acquitted, and his lawyers referred the evidence adduced at the trial to the Director of Public Prosecutions.

Wilde left the court at noon on the fifth of April, 1895 and was arrested at 6:30 PM that evening. There is no doubt that he could have fled the country, and was indeed advised to do so, but he vacillated helplessly, and the last train for the continent left without him. At his trial, the jury could not agree on a verdict, but on retrial, he was convicted of committing "acts of gross indecency" and sentenced to two years hard labour. In passing sentence, Mr Justice Wills said that it was the worst case he had ever tried, accused Oscar Wilde of being "the centre of a circle of extensive corruption of the most hideous kind," and added that he was "expected to pass the severest sentence that the law allows" although it was "totally inadequate for such a case as this."[12]

Broken in spirit and health upon leaving prison, Wilde went to France and died there in 1900. The cause of his death has been attributed to neurosyphilis or to an intracranial suppuration from otitis media. He had sustained an ear injury in prison with subsequent and recurrent drainage.[13] His bones were reinterred in the famous Père-Lachaise Cemetery in Paris in 1909.

In 1912, Jacob Epstein, then an avant-garde sculptor, was commissioned to create a suitable tombstone for Oscar Wilde; his response was to hew an immense winged sphinx from a 20-ton block of Hopton Wood stone. This was transported to Paris and placed over Wilde's grave, but the nakedness of the sphinx's genitals was considered indecent by the Paris gendarmerie, who refused to let Epstein complete his work.[14] There is a story, perhaps apocryphal, that two English ladies were so incensed by the tombstone's offending organs that they stoned them, some of the chips ending up in the cemetery office as paperweights!

Oscar Wilde was bisexual, and his marriage in 1884 was followed by the birth of two sons within two years. No satisfactory explanation of his deviation has been given, and theories still abound to explain it, as indeed they do for all homosexuality. Suffice it to say that in the 1890s—the decade of "decadence"—licence of all kinds was condoned by the followers of aestheticism, and Wilde, who was no drinker or drug taker, suffered the penalty of being branded with the most heinous offence of all in Victorian eyes. Had he ignored Queensberry's action, he might well have continued his career in peace, as did many of his "decadent" colleagues, despite their excesses.

That Oscar Wilde has been forgiven by society became evident in 1954, the centenary of his birth, when the London County Council unveiled a plaque affixed to the wall of the house he occupied at the time of his trials. Appropriately, the ceremony was conducted by Sir Compton Mackenzie, the flamboyant author, who once said, "All my life I've lived hand to mouth. Damned good hand to mouth, mind you."[15]

What is to be learned from repeating the tale of Oscar Wilde? Perhaps only that the unusually harsh penalties imposed on homosexuals must now be redressed by an enlightened humanity. Today, consenting homosexuals may live together openly in Britain; in this country, prosecutions of homosexual offenders have become rare, and as a recent *Time* essay said, "It is true that America has a great deal to be ashamed of in its treatment of homosexual citizens . . . . The best public policy toward homosexuals is no policy at all—no sodomy laws, no special interventions pro or con. On matters of consensual adult sex, the law is, or should be, blind."[16]

The words that Oscar Wilde wrote to Lord Alfred Douglas from Reading Gaol could today well apply to the world: "Perhaps I am chosen to teach you something much more wonderful, the meaning of Sorrow, and its beauty."[17]

REFERENCES

1. The most specific is PEARSON, J. *Edward the Rake.* New York, Harcourt Brace Jovanovich, 1975.

2. PARTRIDGE, E. *A Dictionary of Slang and Unconventional English.* 7 ED. New York, Macmillan, 1970.

3. *Brewer's Dictionary of Phrase and Fable* (Rev. Ivor H. Evans). New York, Harper and Row, 1970. "A gay Lothario . . . a seducer of women . . . from Rowe's . . . *The Fair Penitent* (1703)."

4. The indictment against the Marquess of Queensberry in the first trial said that he had libeled Wilde by ac-

cusing him "of committing the abominable crime of buggery with mankind to the great scandal and disgrace of the said Oscar Fingal O'Flahertie Wills Wilde to the evil example of all others in the like case offending and against the peace of our said Lady the Queen Her Crown and Dignity" (Quoted from 12). The entry under "ABOMINABLE CRIME" in a recent reference work reads "Formerly used in Acts of Parliament in Referring to Buggery." (Scott, Sir H. *The Concise Encyclopedia of Crime and Criminals.* New York, Hawthorn, 1961.)

5. STEVENSON, RS AND GUTHRIE, D. *A History of Oto-Laryngology,* Edinburgh, Livingstone, 1949.

6. The Bronte sisters published their first works under male pseudonyms, and George Eliot's real name was Mary Ann Evans.

7. Willie Wilde became a journalist and lived in New York after marrying Mrs Frank Leslie, the owner of *Leslie's Illustrated Newspaper.* She soon divorced him and he died in London in 1898.

8. Isola Wilde died in 1867.

9. HYDE, HM *Oscar Wilde.* New York, Farrar, Strauss and Giroux, 1975.

10. Whistler himself was involved in a libel suit against John Ruskin who had written scathingly of one of his works. As in Sir William Wilde's case, he was awarded 1/4 d in damages.

11. "Q," an accomplished lightweight boxer, drew up his rules in 1866 with another aristocratic sportsman, Lord Lonsdale, and John Graham Chambers of the London Amateur Athletic Club (often confused with Arthur Chambers, lightweight champion of the world).

12. HYDE, HM *The Three Trials of Oscar Wilde.* New York, University Books, 1956.

13. CRITCHLEY, M. Oscar Wilde. A Medical Appreciation. *Medical History,* 1, 299, 1958.

14. EPSTEIN, SIR J *Epstein: An Autobiography.* 2 ed. London, Vista Books, 1963.

15. *Daily Telegraph.* London, 29 August 1973.

16. LEE, J. Homosexuality: Tolerance vs. Approval, *Time,* 113, 48, January 8, 1979.

17. HART-DAVIS, R. *The Letters of Oscar Wilde.* New York, Harcourt, Brace and World, 1962. Wilde's letter was published as *De Profundis* and contains his account of his relationship with "Bosie."

Medicine in Retrospect

[The following is a transcript of an informal talk by Drs Kinloch Nelson and Charles M. Caravati, presented in 1974 to the School of Medicine of the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia.]

Dr Caravati:

One of my first recollections while I was a medical student was the severe pandemic of influenza of 1918 and 1919. There were in excess of a thousand patients at one time in the John Marshall High School, which was used as an emergency hospital. The death rate was terrifically high; the most serious complication was empyema, but most of the deaths were apparently caused by betahemolytic streptococcus infection superimposed upon the influenza pneumonitis. The medical students acted as orderlies in the temporary hospital.

If you went on the wards of St Phillips or Memorial Hospital in those days, you would find any number of cases of typhoid fever between July and September; there was no therapy for it, and in many patients it was fatal. Malaria was common until the end of August. As people went to the seashore, many of them developed malaria.

In the winters, pneumococcal pneumonia was a very common disease. All we really knew about it was how to diagnose it. There was nothing we could do for it except [to take] general measures and to comfort the family and have a good nurse on the job. It is interesting to recall that during the influenza epidemic, the Richmond Health Department stated the only worthwhile medicine was whiskey.

In 1934 a type specific serum came into use, which was very effective for certain specific types of pneumococcus. The health department had a typing station where we could have the sputum typed promptly, but the severe reactions encountered [by the patients] kept a lot of physicians from using it because of its potential anaphylactic effect.

Childhood diseases were serious and prevalent. The most fatal in those days was laryngeal diphtheria, and some of us were trained to intubate for this complication. Interestingly enough, laryngologists never did it. Dr Lipscomb, a general practitioner, was an expert intubator. He saved many lives by using laryngeal tubes.

There were very few drugs that were of any real help, although some newer ones were being developed and used. For instance, Salvarsan and bismuth were being used for syphilis. At that time, too, we were beginning to realize that specific vitamins helped some of the disorders we were seeing, particularly those in children.

When I was a freshman medical student, Dr Joseph Goldberger of the Public Health Service came and talked to the profession about pellagra and explained that a good general diet and nicotinic acid would cure it. I remember very well his making the statement that more than 300 people had died of pellagra that year.

Then came one of the great breakthroughs in medicine—the discovery of insulin by Banting and Best in Toronto in 1922. This was the first time, I believe, that a cooperative therapeutic effort was made by the medical profession and a pharmaceutical manufacturer. Eli Lilly co-produced the insulin for Banting and Best, which was later distributed to doctors in designated regions of the country by a physician in each region, who had to be provided with the proper protocol for its use.

In Richmond we had to apply for insulin to Dr Lester Newman, a pathologist in Washington, DC. I had come back to Richmond in 1924 to practice, and I had been here only a few months when I went to Sheltering Arms Hospital and saw a four-year old child in diabetic coma. It was the second episode of coma she had had, and I remember speaking to Dr Newman

on the telephone and trying to persuade him to send me insulin without a protocol.

Eventually he agreed and sent some on the RF&P Railroad, and the drug was given to this child the next day. Later, when she was about 30 years of age, she walked into my office one day just to say hello and tell me she was living in Cleveland. That was the first real success in controlling chronic disease that I can recall, and I think it is significant to remember the way it was handled by the profession and pharmaceutical industry.

In 1925 Minot and Murphy discovered that people with pernicious anemia improved on an adequate diet, particularly one with flesh meat and liver. Practically every patient treated in this way went into remission and stayed in remission indefinitely if they were kept on this treatment. I think the original work was done in the latter part of 1925, but we didn't use it clinically until 1926 and 1927.

I recall one female with pernicious anemia, who had been kept alive with frequent transfusions, and the dietician in the hospital ground up some pork liver and started feeding the patient half a pound a day. She went into remission shortly after receiving this new diet and died of a cerebral accident eight years later. It was soon discovered that the active principle in eliminating the anemia was in liver.

Dr William Branch Porter, chairman of the Department of Medicine at MCV, had the Valentine Company of Richmond manufacture an extract from liver, and the company made the first extract that was for sale in America. It was called Valentine Extract E-29, and it was a very effective treatment. It took about one ounce of the oral extract each day to control the anemia. The rest of the story, as you know, was the discovery of B-12 as the active principle.

Not long after this we found out that brucella abortus and tularemia, which were originally thought to be diseases in animals, could cause human disease, and we began to diagnose a few cases in this area, though frankly there were very few cases in Richmond or even in Virginia.

Endocrinology was beginning to be talked about at this time, and the active principle of the parathyroid gland was isolated. Between 1932 and 1934 Barr, who was professor of medicine at Barnes in St Louis, and later at Cornell, described the clinical symptoms of hyperparathyroidism and how it could be cured by the removal of the adenoma in the parathyroid gland. He showed that after surgery the cystic changes in the bones went away, and the biochemical changes all went back to normal. This work led to the treatment of certain cases of hypoglycemia by the removal of a pancreatic adenoma.

In 1937 ergotamine-tartrate was reported by Lennox as effective treatment for migraine headaches, and we thought this was a great thing because previously there was nothing a physician could do for these people except put them to bed, pull down the shade, and let them stay there, nauseated and vomiting, for three or four days.

In Germany in 1935, Domagk found that certain sulfonamides were very effective against betahemolytic streptococcal infections. In this country in 1936, it was recognized by the profession as a powerful anti-infectious agent.

The first drug was called Prontosil, a sulphanilamide that came in the form of a red half-gram tablet. With the possible exception of quinine for malaria and of Salvarsan, which was used for the treatment of syphilis, this sulphanilamide was the only specific drug used to treat infections.

I remember seeing a 36-year old man with a temperature of 104° or 105° F with a membrane in his throat and cervical lymphadenopathy and betahemolytic streptoccus infection of his throat, which two days later became a bloodstream infection. At that time Prontosil had just been developed, and it was given to this man who had difficulty in swallowing the first couple of tablets.

He stayed sick for another two days, but in 48 hours his temperature began to come down, his tachycardia disappeared, and he was considerably better in five to seven days. In those days we didn't repeat blood cultures, but clinically he became well. After that, Sulphathiazole, Sulphadiazine, and Sulphapyridine came into use, Sulphapyridine being an excellent drug for pneumococcal pneumonia.

Though penicillin was discovered by Fleming in 1929 and subsequently purified by Florey and Chain in Oxford, it was translated into clinical usefulness by scientists at the North Regional Laboratories in Peoria, Illinois. Penicillin was made available during World War II, and its distribution was directed by Dr Chester

Keefer of Boston. In the beginning it was used only for gram-positive infections.

Dr Nelson:

What I am going to say is somewhat autobiographical. I came back here [to Richmond] to practice medicine at the McGuire Clinic on July 1, 1929, at a salary of $150 a month. In October, 1929, the roof fell in! St Luke's Hospital usually had 85 to 90 patients. The cut-off point was around 65 or 66, as I understood it; at that level you came out about even. Anything above that was nice, but anything below that was real tough.

The hospital population dropped off almost immediately to around 20 where it stayed for several years. Through the kindness of Dr Stuart McGuire, the institution held together, and my salary was gradually reduced to $112.50 a month. I never knew why I got the 50¢, but I never asked anyone.

Mr Roosevelt came into office and started the WPA and the CWA and those other federal agencies that created work, one result of which was the building of the Lee Bridge. The number of physicians applying for the opportunity to examine the workmen who would build the Lee Bridge was out of this world. The man responsible for these funds was Dr Wyndham Blanton, Sr, the present Dr Wyndham Blanton's father, who was recognized for his general overall integrity, so he was given the task of deciding who would examine these birds!

Well, I was one of the early applicants, and it was finally decided that we would each work a certain number of shifts. We examined the workmen at the rate of 50¢ apiece. We could examine one man in fifteen minutes across the street from here in the basement of the City Hall Annex, which was recently pulled down.

Shortly before this, the physicians of this area began to realize that the best possible arrangement they could have was to work in groups. I think the McGuire Clinic group was one of the first to organize, and there was some criticism of this because doctors thought they should stand on their own feet and not associate with a group. This led to the question of whether a patient could "get a square deal" in a group. It seemed to me then and now, that there is no better doctor/patient relationship than that in which the patient picks out his doctor for whatever reason.

There was one lady who was going to a doctor whose capacity was certainly rather indifferent. I asked her why in the world she picked out this fellow. She said he looked more like a bulldog than any other doctor she'd ever seen. Well, on this basis he had her confidence, so she'd tell him her problems, which he attempted to take care of. She expected to pay, and he expected her to pay, and you can't beat that. In my opinion there isn't any other system that will ever equal that, but we have to play it the way it is.

There was interest about that time in the care of the indigent of the City of Richmond, and Dr B. Foster of the Health Department suggested that I take on the job as doctor to the poorhouse. To tell you the truth, I didn't exactly know where the poorhouse was, but I ended up there working part time at $50 a month. Added to the $112.50 [I was already making at McGuire Clinic], this was a considerable increase, and things seemed to be getting better.

There used to be an idea that the physician had a certain responsibility to the poor. Some physicians had office hours at certain times of the week for those who could not pay in the same office in which, at other times, they saw those who could pay.

We seem to have shifted away from that feeling of taking care of the overall population. It has somehow become the responsibility of somebody else to take care of those who cannot pay. It is interesting to remember that there once seemed to be a shortage of patients. A group opened an office with the idea of helping out in an indigent area. Shortly, the patients didn't seem to be there, and they had to close down. This was an odd circumstance.

After the second World War, I think the most striking thing that took place was the development of the "medical center." The medical school had, of course, been well known for many years, and everyone knew something about the teaching of medical students and to some degree [had knowledge of] the housestaff and nurses.

There was the necessity for employing faculty members to take care of many obligations besides direct patient care and teaching residents and students. This was hard to get across to people. All of these concerns have

brought about full-time physicians who, in many instances, have never really practiced medicine—have never really gotten down to the nitty gritty. This makes it difficult for them to understand the problems of the practice of medicine, and, on the contrary, those in practice have difficulty in understanding the problems of the faculty members who are in "the ivory tower."

These divisions have led to a lot of problems, but they are not new. If you go back in the history of the Medical College, you will find some of the most remarkable fights you ever saw in your life that took place before the 1900s. In the meantime, it appeared to me that the medical student and housestaff member were somehow divorced from the practice of medicine and consequently were not "interested" in practicing medicine. Now, this is baloney because the statistics show something like 90-odd percent of the graduates of this school have gone on to practice medicine.

Back in 1950, Dr Sanger managed to get some money to allow us to rotate our housestaff through community hospitals, and we sent them to four or five—I think Eastern Shore, Franklin, Farmville, Fredericksburg, and Norfolk, but this created some problems. These boys were, for the most part, married, which, as you know, is one of the greatest changes to take place in medical education.

When I was a student, nobody was married. There was one fellow who was married—incidentally, his wife had a baby, which was the biggest surprise all of us ever had. We were senior medical students and saw this lady everyday, and if you had asked me the day before she had the baby whether she was pregnant or not, I would have said no.

In any case, through Dr Sanger's influence we began to try introducing the housestaff and students to some of the actual practice situations that exist in this neighborhood. After rotating the interns through the hospitals, we started a Home Care program, for which we obtained money through the Commonwealth Fund. The idea was for medical students to see something that took place in actual life.

Unfortunately, this was not exactly actual life. This was life of a sort, but many physicians today never see patients such as those that were seen in Home Care then. These were people who lived in half a barrel over here on the city dump and had no money and no anything. How they ate, lived or whatever, nobody knew. You don't see patients like that in your practice—at least, I hope you don't. Then we put students out in the affiliated hospitals, very much the same hospitals as we sent the interns to 20 years ago, plus a few more.

There are a couple of other things that stand out in my mind as developments over the years. I remember one difference is that now if you call a doctor, sometimes nobody answers the telephone. This seems remarkable. If you called a doctor in 1930, about four people would answer the phone. Even today a ringing telephone gives me the jitters because I'm not sure whether it is somebody who really needs something or somebody that I need. I cannot imagine how it is possible to practice medicine and have an office that [allows telephone calls to go unanswered], but it can be done, and it is.

The second thing that bothers me is the idea of telling everybody everything. I was raised on the principle that the doctor knew best, and the patient didn't know anything, and the better off he would be if he didn't know any more. I am not sure but what this is right. I think this business of advising everybody of all the details of all the problems that they have or may have is really bad. I don't know what you do about it exactly, but I can tell you what I have done about it.

I was called one night to see a man who had, as far as I could see, a coronary thrombosis. So I went back to the office and got the electrocardiogram machine which took three leads—three, not twenty-three—and went back to his house. According to the three leads that ran out of the thing, it looked to me like he had a coronary thrombosis. So I told him I had to go back to the office to develop the film.

Well, this didn't make much sense as it was coming right out of the machine, but it suited him all right, so I went back and developed the film, and while I was there I got a normal electrocardiogram. I went back [to his house], and he said, "How does that thing look?" I said, "Boy, it looks fine to me. Here it is. You want to see it?" He said, "Well, I don't know anything about those things," and I said, "That doesn't make any difference. I'll show it to you."

So I pointed out the normal pulse waves and QRST, and he started feeling better right away. I didn't do him any harm, I think, and

I don't see what good it would have done for me to tell him how it did look by saying, "Boy, you've got it!" Now, I do think you ought to tell the patient's wife or son or whoever is responsible.

Another thing that interests me is that I believe the AMA or somebody has decided that we are short 50,000 doctors. I don't know how they arrived at that figure; there's some complicated calculation which shows that if you graduate all the doctors who are graduating, and all those who have died or are dying, and none die unexpectedly or in an epidemic, in some unknown year in the future we will reach the necessary number of doctors, whatever that means. I think that's "for the birds."

I think that in your lifetime, and hopefully mine, we will have doctors coming out of our ears. By the time the doctors now being graduated by medical schools, plus those who will shortly begin to do so, plus the trained personnel now going on in various things like physicians' assistants, nurse practitioners, med-x, and so forth, we will have an excess of people doing first-line medical care. It is a supply and demand business, and I hope I live to see that.

Discussion

Question: Who is the greatest medical character you remember in Richmond?

Dr Nelson:

I can think of one doctor I won't name who was always referred to as the "cheerful little cricket." To my knowledge he never smiled in his life. Oddly enough, his patients seemed to love this very sad approach; everything was going downhill all the time, but he had plenty of practice—plenty.

I recall another who was a great crier. In other words, if anybody was very ill or somebody died, and members of the family were weeping, he was the greatest weeper there. Tears ran down his cheeks like a waterfall. He was very popular.

Dr Caravati:

Dr W. T. Oppenheimer was one of the real interesting medical personages of his time. He was President of the Richmond Academy of Medicine in 1900, and he lived about 45 more years. He was an excellent general practitioner, if you want to use that term, and he did general surgery. As far as we know, he did it well. He was the best toastmaster in the area, and every medical meeting was enlivened by him. He would always tell a story, and he always had dozens of them.

Question: Dr Nelson, how about your service in the 45th?

Dr Nelson:

Well, I'm glad you mentioned that. I went into the 45th General Hospital as a major. Why I wasn't made a higher rank I never could understand. Dr Thompson, I believe, was a lieutenant, and in no time at all he became a captain, but I was still a major. Shortly after that, he became a major; I was still a major. Shortly after that, I left the army. I figured I'd done all I could. I couldn't get promoted, so forget it. What Dr Thompson is talking about is that I became ill due to my arduous service and was sent home on a stretcher. As I embarked at Naples, the band came down to see all the poor souls who were going home, and among them were 16 pregnant nurses.

One of them had just had a baby—cutest baby you ever saw. One nurse had arthritis, and she had a lot of x-rays so nobody would accuse her of the problem that the other girls had.

Incidentally, this was the first boat from Naples that came straight back to the States. Prior to this time, wounded and sick troops were sent from Naples to Africa. Sometimes the doctor in Africa was kind of an eager beaver and wanted everybody to serve, so he'd send them back to the front in Naples. Well, they didn't like that, so they worked out a boat to take them straight back to the States.

The chief doctor on this boat was an obstetrician, and he had been in the army for I don't know how long. He hadn't seen a pregnant lady since he got into the army, and we presented him with 16 cases. He nearly had a fit; he was examining people all the way home.

Dr Caravati:

I thought it might be worthwhile just commenting that during World War I many of you may not know the Medical College of Virginia was also the 45th General Hospital under [the direction of] Dr Stuart McGuire, and Dr Nelson's father was one of the prominent members of the staff in 1918. The hospital was in action during

the period of some of the hardest fighting around the Argonne. The history was written by Dr Joseph Geisinger, who was a urologist in town, and it is well worth reading.

Question: Will you comment on the merger of the two schools of medicine in Richmond?

Dr Caravati:

You'll have to remember that geographically the two schools were only two city blocks apart which, of course, should have never been. All the faculty were part time, and the faculty members in the two schools practically never spoke to each other. They had very strong feelings about this, but perhaps the competition made for good medicine because they tried to outdo each other when they made scientific presentations.

In 1910 the Flexner Commission found that they were graduating too many physicians in the state and recommended the merger of the Medical College of Virginia and the University College of Medicine. After that, there was a fight about twice a week, as I understand it. However, the merger was accomplished in 1913 through the efforts of many outstanding people led by Dr Stuart McGuire, Dr George Ben Johnston, Dr Christopher Tompkins, and Mr Eppa Hunton. Drs McGuire and Johnston were not friends; only as far as their interest in medical education did they get together.

There were a lot of stories about individual physicians and their behavior at meetings. Dr Daniel Coleman is said to have come to a meeting with a pistol on his hip, and no one knew whether he had real bullets in it or not. He stood on a chair and said, "I am not as big as the rest of you, but look here."

Dr Nelson:

The father of Mr Eppa Hunton was really the catalyst between the warring groups and brought them together in the consolidation of the Medical College of Virginia in 1913 more than anyone else.

Question: Do you have any further comments about the care of the indigent patient?

Dr Caravati:

Well, one dramatic example is Sheltering Arms Hospital. Sheltering Arms was for years right over here on Clay Street. Now it is adjacent to Richmond Memorial Hospital. In days gone by, every doctor thought it a privilege to be able to take care of patients at Sheltering Arms. I know we all thought it was a great thing to be on the visiting service, and also to teach the nurses; we really did think it was a privilege to do all this. No doctor ever received a penny for his services, nor did any patient pay for his or her care.

Question: Have you seen anything in medical education that has changed, or is educating doctors about the same as when you were in school?

Dr Nelson:

Everything has changed. I was thinking the other day about Dr W. B. Porter. Dr Porter was a very handsome person, and he was very concerned about his appearance; he always had on a spotless white coat and a little flower in his buttonhole. He had the idea that he ought to look like a doctor—whatever that means. Were he to see some of our present campus candidates, I'm sure he'd be revolving wherever he is.

The most remarkable change I have seen has been in the last four or five years. Everyone seems to be going into primary medical care, which I think is a very salutary move. It's hard for me to tell, you see, because I was raised as a doctor. My earliest recollection is over here in the old Memorial Hospital with my father, sitting in the waiting room while he went to see a patient or two. I can remember the horse he had named Phyllis. Every now and then Phyllis would take it into her head to go home. When we would come out of wherever we were, there was no horse.

Dr Caravati:

One development that has been interesting to me is that now you can't find a doctor to come to your home. Most patients can be transported to an emergency room in one of the hospitals. Probably 50 percent of the patients seen there are not true emergencies. Because of well qualified physicians who are full time, good care is administered in an excellent setting. This makes many house calls unnecessary, and I believe this practice will grow rapidly. To me it is a really interesting evolution of

the practice of medicine, and I think it is going to continue to grow.

Dr Nelson:

I would like to put in a plug for house calls. If you have an occasion in your practice to see a patient in the home, I would recommend it. There is no better place you can get to know them as well, and it has always struck me as odd that when you get into the home, about the only private spot is the bathroom. If you want to talk to the wife about the husband, you just call her into the bathroom and shut the door, and nobody else will come in there.

Dr Spencer:

Thank you very much indeed, Dr Nelson and Dr Caravati. You have shown that history doesn't have to be dull and uninteresting, and I am delighted that you could tell us about your 50 years of practice. Thank you very much again.

Dr. Nelson is Dean Emeritus and Dr. Caravati, Professor of Medicine Emeritus, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia.

Recent Advances in Cancer Chemotherapy

ROBERT B. DIASIO, MD

Associate Professor of Medicine and Pharmacology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

The present status of cancer chemotherapy can be reviewed in light of selected basic principles with an acknowledgement of the role of established chemotherapeutic agents. Four chemotherapeutic agents recently approved for clinical use and their impact when used in combination regimens should be examined. Several important concepts influencing chemotherapy in the 1980s include the use of chemotherapy in the adjuvant setting, the use of hormonal receptor data in planning therapy, and the use of *in vitro* tests on tumor specimens to predict tumor sensitivity to cancer chemotherapy drugs (prior to administration of these potentially toxic drugs to a particular patient). Lastly the reader is cautioned about the potential of long-term complications with certain chemotherapy agents, especially in those patients who have had complete or extended partial remissions.

Review

The modern era of cancer chemotherapy began approximately 40 years ago when nitrogen mustard, a derivative of the mustard gases used in the World Wars, was demonstrated to cause regression of lymphomatous tumors initially in studies involving mice and later man. Since that time a variety of chemicals and natural products have been synthesized (or isolated) and subjected to various screening programs in an attempt to identify potential clinically-effective drugs. Today there are approximately 30 drugs that have been approved and deemed valuable in the treatment of various human cancers.[1] These agents can be categorized into six major classes (Table 1).

The development of these diverse agents which effect various critical biochemical steps or processes has occurred during a period in which there have been rapid and significant gains in our understanding of the molecular biology of the cell. Concomitantly, there has been an increased understanding of tumor cell biology which has markedly influenced the way cancer chemotherapy drugs are used today. Cell kinetic studies in animal models have demonstrated that a single malignant cell can multiply within a host animal to eventually kill the host. Thus curative therapeutic approaches must aim to eradicate every malignant cell. Studies with anticancer agents in animal models have shown that chemotherapy kills cells in a first-order kinetic manner, *ie,* with each treatment a constant percentage (rather than a constant number) of cells is killed. These generally accepted "principles" have provided support for the aggressiveness now used in many of the multiagent chemotherapy regimens and have formed the basis for adjuvant and maintenance chemotherapy.[2]

Multiagent, or combination chemotherapy, the major approach used in advanced cancer today, has been influenced by a better comprehension of the cell cycle. Thus it is recognized that certain drugs act on cells only in a specific phase of the cell cycle (the life cycle through which a cell passes from its origin when formed from the mother cell to the point at which it in turn divides into daughter cells) while other drugs are non-cycle specific, being able to affect cells regardless of where they are in the cell cycle, including cells not actively replicating. The recognition of this concept has been utilized in designing effective combination regimens which aim at affecting cells in different

TABLE 1
Classification of Cancer Chemotherapy Agents

Alkylating Agents
- Mechlorethamine (Mustargen)
- Cyclophosphamide (Cytoxan)
- Chlorambucil (Leukeran)
- Melphalan (Alkeran)
- Triethylenethiophosphoramide (thiotepa)
- Nitrosoureas
  - (BCNU or Carmustine)
  - (CCNU or Lomustine)
  - (5-(3,3-Dimethyl-1-triazene)-imidazole-4-carboxamide)
  - (Dacarbazine or DTIC)

Antimetabolites
- Methotrexate
- 5-Fluorouracil (Fluorouracil, Adrucil)
- Cytosine arabinoside (ara-C or cytosar)
- 6-mercaptopurine (Purinethol)
- 6-thioguanine (thioguanine)

Antibiotic
- Dactiomycin (actinomycin D. (Cosmergen))
- Mithromycin (Mithracin)
- Doxorubicin (Adriamycin)
- Daunorubicin (Daunomycin)
- Mitomycin C (Mutamycin)
- Bleomycin (Blenoxane)

Natural Products
- Vinblastine (Velban)
- Vincristine (Oncovin)
- L-Asparaginase (Elspar)

Miscellaneous Agents
- o,p'—DDD (Mitotane (Lysodren))
- Hydroxyurea (Hydrea)
- Procarbazine (Matulane)
- Cis-platinum diamine dichloride (Cisplatin, Platinol)

Hormones
- Estrogens
- Androgens
- Progestational Steroids
- Adrenal Steroids
- Antiestrogen tamoxifen citrate (Nolvadex)

phases of the cell cycle to obtain the maximum therapeutic effect.

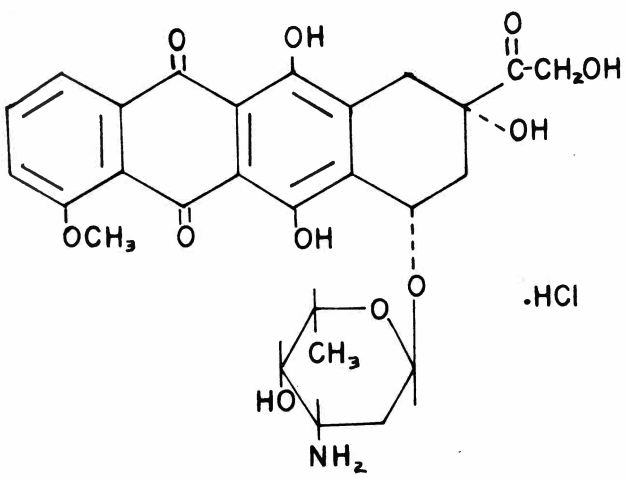
The success of chemotherapy in the management of human cancer can be seen in Tables 2 and 3.[2] Table 2 demonstrates that in at least seven tumor types, chemotherapy now offers either cure or at the very least a significant prolongation of life. While actual cure has not been achievable for the five tumors listed in Table 3, there nevertheless has been a demonstrated increased survival and palliation. For the remaining tumor types not listed, including the relatively frequent cancers such as carcinoma of the lung and large bowel, cure and palliation are less likely at present. With the development of new agents, it is hoped that more effective combination regimens will be created to improve survival in these currently less responsive tumors as well.

Update

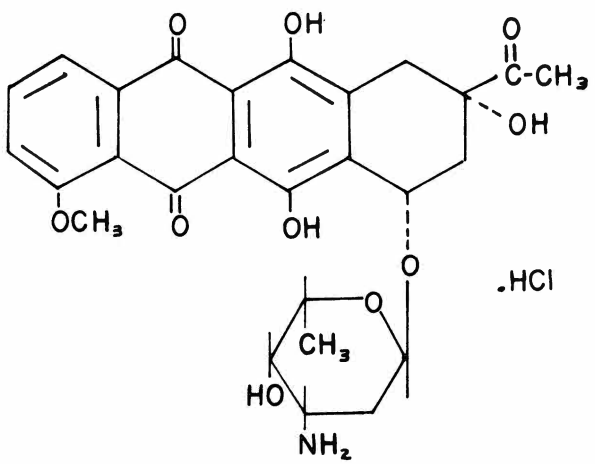
Over the past several years there have been four new agents introduced clinically that are now not only approved for non-investigational use but also occupy important roles in cancer chemotherapy already. The increasing use of all four drugs necessitates a basic understanding of them by every physician participating in the care of a particular cancer patient.

Doxorubicin (Adriamycin)

Perhaps the most important new agent is Adriamycin. This drug and the closely related drug Daunorubicin (Daunomycin) are anthracyclene derivatives obtained as fermentation products from *Streptomyces* (Fig 1). These



Adriamycin



Daunomycin

Fig. 1.

TABLE 2
Cure or Increased Survival

Type of Cancer	*Chemotherapy*	*Results*
Gestational trophoblastic tumors	Methotrexate, dactinomycin, vinblastine	70% cured
Burkitt's tumor	Cyclophosphamide (many others)	50% cured
Testicular tumors (nonseminoma)	Dactinomycin, Methotrexate chlorambucil, Bleomycin, Cis-platinum diamine dichloride	70–80% respond; 2–3% cured
Wilms' tumor	Dactinomycin plus vincristine with surgery and radiotherapy	30–40% cured
Neuroblastoma	Cyclophosphamide with surgery and/or radiotherapy	5% cured
Acute lymphoblastic leukemia	Daunorubicin, prednisone, vincristine, 6-mercaptopurine, Methotrexate, BCNU	90% remission; 70% survive beyond 5 years
Hodgkin's disease, stage IIIB and IV	MOPP, ABVD	70% respond; 40% survive beyond 5 years

(*Note*: Adapted from I H Krakoff, Cancer Chemotherapeutic Agents, *Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.) **(By Permission)**

drugs are classified as antibiotic cancer chemotherapy agents.

The mechanism of action of both drugs is believed to be via inhibition of DNA synthesis. These agents are known to interact with DNA, eventually intercalating into the nucleic acid helix leading to uncoiling of the DNA and inhibiting both RNA and DNA synthesis. Both agents are maximally effective during the S phase of the cell cycle, but inhibition can occur at all stages of the cell cycle, particularly at higher concentrations.[3]

The pharmacology of these drugs is still somewhat incomplete. At present they are used only intravenously. The major site of metabolism is in the liver by both soluble and microsomal enzymes. Less than 10% of the drug is excreted in the urine. Because of the importance of liver metabolism, the dose of Adriamycin is reduced in the presence of hepatic dysfunction. No drug adjustments are made for renal dysfunction. The total dose should not exceed 550-600 mg/M^2.[2,3]

Both drugs have similar side effects and toxicities including: 1) gastrointestinal (nausea, vomiting, diarrhea, and stomatitis); 2) hematologic (leukopenia with a nadir at 10-15 days, and thrombocytopenia); 3) dermatologic (alopecia, local phlebitis and necrosis if extravasated); 4) cardiac (by far the most serious toxicity with these drugs is manifested as congestive heart failure due to a diffuse cardiomyopathy).

The major indications for Daunorubicin (Daunomycin) have been in acute granulocytic, and in lymphocytic, leukemia. In contrast, Doxorubicin (Adriamycin) has been active not only in leukemia but also in bladder cancer, breast cancer, bronchiogenic cancer, Hodgkin and non-Hodgkin lymphoma, thyroid cancer and sarcomas in general.

Bleomycin (Blenoxane)

Bleomycin, also of the antibiotic class of chemotherapy agents isolated from *Streptomyces,* is actually a mixture of several similar polypeptides, each having a molecular weight of approximately 1500. The A_2 peptide is the major compound present in the commercial preparation and is believed to be the active component (Fig 2).

The mechanism of action of Bleomycin appears to be by scission of double-stranded DNA, resulting in fragmentation of DNA, in turn causing inhibition of DNA synthesis. This drug appears to block cells at the G_2/M interphase of the cell cycle.

The pharmacology of this drug *in vivo* has been limited by the fact that the drug is a mixture of several compounds. Following administration, it disappears rapidly from the plasma with an estimated half life of 15-60 minutes. Since the drug is known to be excreted primarily via the kidneys, the dose should be reduced in the presence of renal dysfunction. Bleomycin is

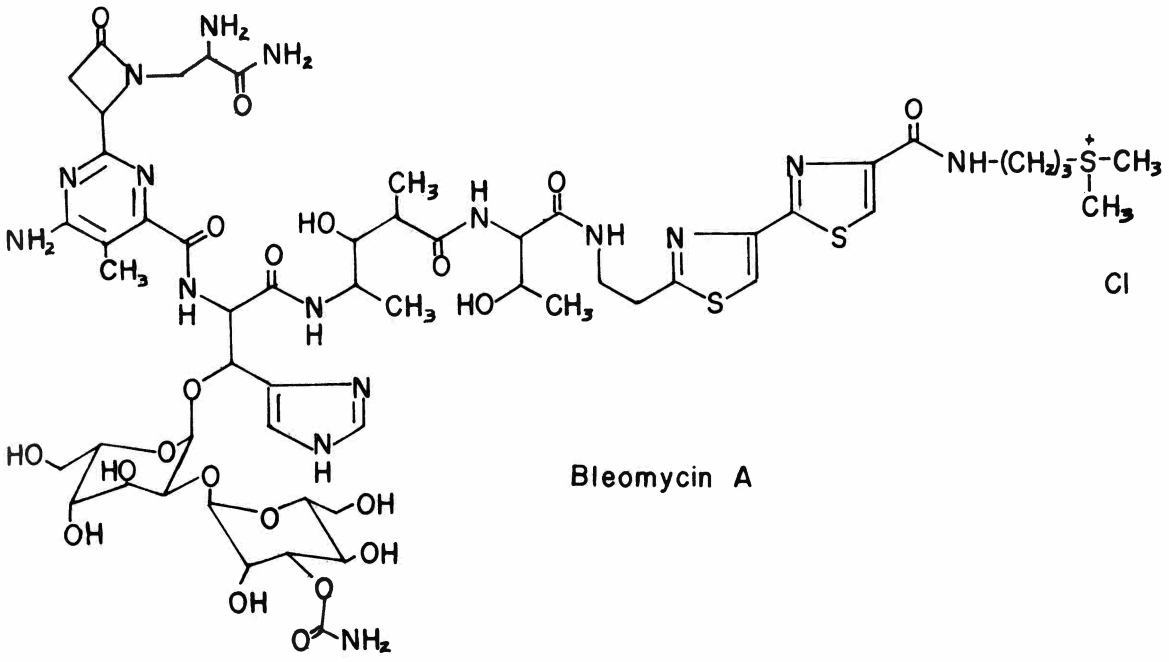


Fig. 2.

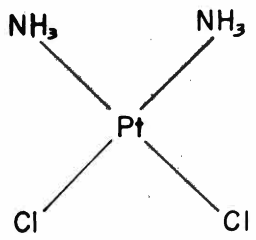
degraded mainly by the action of animonopeptidase which is present in tumor cells, liver and kidney. It is absent from the skin and lungs, two tissues which are particularly susceptible to damage from this drug. Bleomycin is administered either intravenously, intramuscularly, or subcutaneously.[2,3]

As noted above, Bleomycin toxicity includes skin toxicity (such as hyperpigmentation, thickening, ulceration, rash, alopecia, or nail changes) and pulmonary toxicity. This last severe toxic finding may be present as pneumonitis with dyspnea, râles and infiltrate progressing to fibrosis. The occurrence of toxicity need not be related to the cumulative dose although it is more frequent with a total dose greater than 250 units/M^2 or a single dose greater than 25 units/M^2. The risk is increased particularly in individuals more than 50 years old who may have prior lung disease or may have previously been treated with radiation therapy. Pulmonary function tests have not been of value in predicting pulmonary toxicity. A cumulative dose of 400 units is the accepted maximum dose. Since the drug is a polypeptide, a potential side effect with this agent is anaphylaxis. Fever and chills

TABLE 3
Palliation and Prolongation of Life

Type of Cancer	*Chemotherapy*	*Results*
Prostate carcinoma	Estrogens, castration, cyclophosphamide	70% respond with some prolongation of life
Breast carcinoma	Androgens, estrogens, alkylating agents, 5-fluorouracil, vincristine, prednisone, Methotrexate, Adriamycin	60–80% respond with probable prolongation of life
Chronic lymphocytic leukemia	Prednisone, alkylating agents	50% respond with probable prolongation of life
Lymphosarcoma	Prednisone, alkylating agents	50% respond with probable prolongation of life
Acute myeloblastic leukemia	Cytosine arabinoside and thioguanine	65% remission with prolongation of life

(Note: Adapted from IH Krakoff, Cancer Chemotherapeutic Agents, *Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.)
(By Permission)



cis-Diamminedichloroplatinum

Fig. 3.

occur in 20-30% of patients. The possibility of hypersensitivity is particularly a problem in lymphoma. Nausea and vomiting may also occur with administration of Bleomycin. One toxic manifestation notably absent with this chemotherapeutic agent is the lack of hematologic toxicity making this drug especially appealing for combination chemotherapy.

The major indications for Bleomycin have been in lymphomas (Hodgkin and non-Hodgkin), testicular tumors, and squamous cell carcinoma of the head and neck. Other indications are less clear at this time.

Cis-Diamminedichloroplatinum (Cis-platinum, Platinol)

This agent is a heavy metal coordination complex of platinum containing two ammonia groups and two chlorines in the Cis conformation (Fig 3). It is listed as a random synthetic type of chemotherapeutic drug. The mechanism of action appears to be through inhibition of DNA synthesis thought to result from both interstrand and intrastrand crosslinks in DNA. It appears to be cycle non-specific.

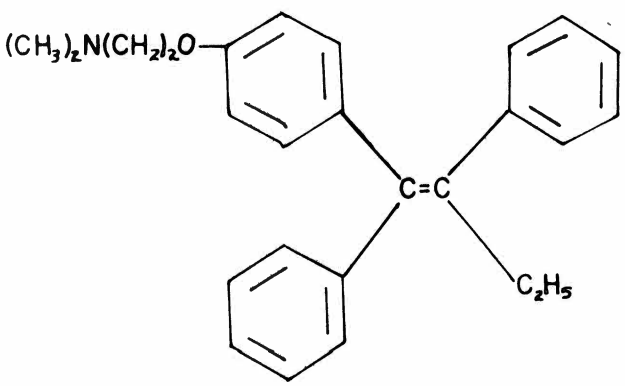
Cis-platinum is administered in an intravenous solution usually in an infusion from 15 minutes to eight hours. Following administration, plasma levels of the drug show a biphasic pattern of decay with an initial half life of 25 to 50 minutes and a terminal half life of 58 to 72 hours. Studies of distribution have demonstrated the greatest uptake in the excretory organs, ovary, and uterus. More than 90% of the platinum following administration is protein bound. Cis-platinum is excreted mainly via the urine. This drug should be used with caution or even withheld if renal dysfunction occurs with a creatinine clearance of <60 ml/min. An attempt has been made to minimize renal toxicity secondary to Cis-platinum administration by hydrating the patient prior to drug receipt, giving diuretics and infusing chemotherapy slowly.

The renal toxicity appears to be dose related. Close follow-up of BUN, creatinine, and uric acid, and particularly creatinine clearance is advisable. Other side effects include ototoxicity, relatively frequent nausea and vomiting, leukopenia, thrombocytopenia, and anemia. Anaphylactic reactions have been described in no more than 1% of the patients given this drug. Peripheral neuropathies and loss of taste are less common side effects.[4] This drug appears to be active in testicular tumors, ovarian cancer, bladder cancer, and head and neck cancer.

Tamoxifen Citrate (Nolvadex)

Tamoxifen is a synthetic non-steroidal triphenylethylene derivative that has been demonstrated to have potent anti-estrogen activity in several mammalian species. It is classified as a hormonal type of chemotherapy agent (Fig 4). The mechanism of action appears to involve inhibition of estrogen binding to cyctoplasmic estrogen receptors present in sensitive cells such as breast cancer. It is believed that following binding to the receptor, estradiol-estrogen receptor formation is blocked. Since this receptor is necessary for activation of certain nucleic acid processes, the hormonal response of these cells is blocked.

This drug is given orally in 10mg tablets. Following oral administration, peak levels occur within four to seven hours. The initial half life is estimated to be from seven to 14 hours. Pro-



Tamoxifen

Fig. 4.

longed blood levels may therefore occur. This is thought to be due to concentration and excretion into the bile tract with reabsorption through the enterohepatic circulation.

Toxicity due to antiestrogenic actions include hot flashes, vaginal bleeding, menstrual irregularities, and pruritis vulvae. Non-specific gastrointestinal side effects have been described such as nausea, vomiting and distaste for food. Other toxic manifestations may include fluid retention, hypocalcemia, and dizziness.[5]

The major indication at present is in palliative treatment of advanced metastatic breast carcinoma. The use of this drug in estrogen-receptor positive premenopausal women with breast cancer is currently being evaluated by the National Surgical Adjuvant Breast Project.

New Combinations

The addition of these new agents has made possible new combinations taking into account not only the principle of cell cycle and cell kinetics suggested earlier, but also permitting modification of toxicity since many of these new agents have toxicity different from many of the standard agents in chemotherapy. For example, Bleomycin and Tamoxifen have essentially no hematologic toxicity and are attractive to use in combination with agents that might cause marked hematologic toxicity. Two particularly interesting new combinations include the ABVD regimen (Adriamycin, Bleomycin, Vinblastine and 5-(3,3-Dimethyl-1-triazene)-imidazole-4-carboxamide) used in Hodgkin disease and the Cis-platinum-Bleomycin-Vinblastine combination used in testicular cancer.[6]

The ABVD combination has been shown to be approximately equally active to the MOPP combination (Mechlorethamine+Oncovin +prednisone+procarbazine) used in the treatment of advanced Hodgkin disease. More importantly, there appears to be little cross resistance of the ABVD regimen with the MOPP combination making possible a suitable alternative treatment for MOPP failures. The combined use of Bleomycin and Adriamycin has also been shown to be active in some recent combinations used in non-Hodgkin lymphomas as well.[7]

In testicular cancers the contribution of these new agents (Bleomycin and particularly Cis-platinum) is even more impressive. While several active agents have been available for many years including Methotrexate, Actinomycin D, and Mithramycin, the percentage of complete remissions was consistently 30% or less with no prolonged survivals. The combination of Cis-platinum-Vinblastine-Bleomycin has resulted in complete remission rates of 70% or greater with an increased percentage of prolonged survivors.[8] The evolution of chemotherapy in the treatment of testicular cancer with first the addition of Bleomycin and later the addition of platinum illustrates the point made earlier that as new agents are introduced in combination with other effective agents, there is hope that still more effective combinations will be found in the treatment of other cancers as well.

Adjuvant Chemotherapy

Adjuvant chemotherapy is usually defined as the use of chemotherapy together with surgery and/or radiotherapy. As suggested earlier, cell kinetics provide a rationale for the use of adjuvant chemotherapy. Following removal of a tumor mass and a curative resection, the cell number should be reduced dramatically. When the cell number is relatively low, tumor cells are more likely to be actively growing and dividing. Since most chemotherapeutic drugs will kill cancer cells actively "in phase" in the cell cycle, it should follow that the smaller the tumor mass, the larger the growth fraction and the more likely the cells are to respond to cytotoxic drugs. The fact that only one cell is needed to theoretically kill the host, and the fact that chemotherapeutic drugs kill in a first-order kinetic manner, further supports the rationale for chemotherapy in the adjuvant setting. A number of experimental studies using mouse and rat tumor models have substantiated the value of adjuvant chemotherapy in prolonging survival.[9]

Clinical trials have now demonstrated a definite role for adjuvant chemotherapy in at least delaying the occurrence of metastases in premenopausal patients with breast cancer. It is still somewhat early to evaluate the overall effect on survival, although it does not appear to be as promising as originally hoped. Two regimens have been used in extensive adjuvant studies in breast cancer in this country and abroad. The American study has utilized the alkylating agent L-phenylalanine mustard, while the European study from Italy has utilized the combination of Cyclophosphamide, Methotrexate and 5-fluorouracil. Both studies have dem-

onstrated a definite role in premenopausal cancer, although the role in postmenopausal cancer is somewhat less clear.[10]

On osteogenic sarcoma there has been a dampening of the original enthusiasm for adjuvant chemotherapy. The initial regimens used during the past five years have included the use of Adriamycin with and without other agents and the use of high-dose Methotrexate. In these studies there has been the suggestion that again metastases may be delayed, but in this case it appears much less likely that any overall improvement of survival has resulted.[9]

For other tumor types the role of adjuvant chemotherapy at present remains much less clear. There is, however, the hope that with newer agents resulting in more effective combinations, there will be increased effectiveness of these drugs used early in the course of the disease with the anticipation that not only the onset of metastatic lesions will be delayed but also that survival time will be prolonged.

Receptor Status

Over the past several years there has been widespread acceptance by the medical and surgical community of the importance of obtaining breast tumor specimens at the time of surgery for assessment of estrogen as well as possibly other hormonal receptors.[11] The estrogen receptor assay has been shown to have a positive correlation greater than 65% with response to hormonal therapy in several large studies recently completed. Furthermore, patients with estrogen-receptor negative tumors appear not to respond to hormonal therapy. The most important impact of this receptor data is that approximately a third of all breast patients with metastasis are estimated not to respond to hormonal therapy. With the use of the hormonal receptor assays, patients who are estrogen-receptor negative may be spared ineffective therapy and may be begun on more effective cytotoxic chemotherapy at an earlier point.

Less clear is the importance of estrogen-receptor negative status in premenopausal patients. Recently it has been suggested in a retrospective study conducted at the National Cancer Institute that estrogen-receptor negative patients may actually respond better to chemotherapy than estrogen-receptor positive patients. This study, however, has been contradicted by yet another retrospective study. At the present time prospective studies are needed to clarify this hypothesis, and no recommendations can be made.[12]

Prediction of Drug Response

For many years there has been the hope that one could test tumor cells, much as one tests bacteria cultured from an infected patient, thereby making a more rational choice of the agent or agents to be used. To some extent this approach has already been adopted in breast cancer where the presence or absence of estrogen receptors in the tumor specimen from a particular patient may determine whether hormonal therapy will be used. Recently a new method was demonstrated which permits tumor cells, obtained from specimens at the time of surgery, to be cultured so that drugs may be tested for possible effect. While only a limited number of cases have been studied at the present time, data in multiple myeloma and ovarian cancers suggest that the possibility exists that indeed a predictive test may be possible,[13] thereby at the very least preventing the use of ineffective cytotoxic drugs and possibly determining effective drugs that may be used in the treatment of the individual patient. Again research will be conducted in the 1980s which will further clarify the usefulness of this new method.[14]

Long-Term Effects of Chemotherapy

While the immediate and idiosyncratic effects of the various chemotherapeutic agents have been well known, it is now clear that some of these drugs, particularly the alkylating agents and those drugs that intercalate into DNA, may result in the development of secondary neoplasms. These usually occur four to five years after the initial chemotherapy has been completed.[15] The implication is that the very patients who have been "cured" by chemotherapy have then gone on to develop neoplasms secondary to the initial chemotherapy. This has now been seen in an increasing number of chemoresponsive tumors; *eg* with the use of alkylating agents in multiple myeloma or with alkylating agents with or without radiotherapy in Hodgkin disease.

The effects of radiotherapy have long been known to be associated with secondary neoplasms so that patients receiving radiotherapy and chemotherapy with agents which

interfere with the DNA structure may be especially at risk. With the development of more effective combinations, it is hoped that some of the agents responsible for these catastrophic toxicities may be removed and replaced by "non-carcinogenic" drugs.

Lastly, there will be a need to review the use of certain potentially "carcinogenic" agents in adjuvant regimens, especially in those patients who may indeed have been cured by surgery. With more experience it is hoped that the more toxic agents may be removed from these combinations as well.

REFERENCES

1. ABRAMOWICZ, M (Ed) Cancer chemotherapy. *Med Lett Drugs Ther,* 20, 19 (Issue 514), 81–88, 1978.

2. KRAKOFF, IH. Cancer chemotherpeutic agents. *Ca-A Cancer Journal of Clinicians,* 27, 130–143, 1977.

3. CHABNER, BA, MEYERS, CE, OLIVERIO, VT. Clinical pharmacology of anticancer drugs. *Semin Oncol,* 4, 165–191, 1977.

4. ROZENCWEIG, N, VON HOFF, DD, SLAVIK, N, MUGGIA, FM. Cis-diamine dichloroplatinum (II), a new anticancer drug. *Ann Intern Med,* 86, 803–812, 1977.

5. HEEL, RC, BROGDEN, RM, SPEIGHT, JM, ET AL. Tamoxifen: A review of its pharmacologic properties and therapeutic use in the treatment of breast cancer. *Drugs,* 16, 1–24, 1978.

6. CAPIZZI, RL, KEISER, LW, SARTORELLI, AC. Combination chemotherapy: Theory in practice. *Semin Oncol,* 4, 227–253, 1977.

7. BONADONNA, G, ZUCALI, R, MONFARDINI, S, ET AL. Combination chemotherapy of Hodgkin's Disease in Adriamycin, Bleomycin, Vinblastine, and Imidazole Carboxamide versus MOPP. *Cancer,* 36, 252–259, 1975.

8. EINHORN, LH, DONOHUE, J. Cis-diamminedichloroplatinum, Vinblastine, and Bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med,* 87, 293–298, 1977.

9. DEVITA, VT. Adjuvant therapy—an overview, adjuvant therapy of cancer (SE Salmon and SE Jones, eds). *Adjuvant Therapy of Cancer,* 613–641, 1977. Elsevier/North-Holland Biomedical Press, Amsterdam.

10. CARTER, SK. Adjuvant chemotherapy in breast cancer: Critique and perspectives. *Cancer Chemotherapy and Pharmacology,* 1, 187–195, 1978.

11. BAXTER, JD, FUNDER, JW. Hormone Receptors. *N Engl J Med,* 301, 1149–1159, 1979.

12. LIPPMAN, ME, ALLEGRA, JC, THOMPSON, EB, ET AL. The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. *N Engl J Med,* 298, 1223–1228, 1978.

13. SALMON, SE, HAMBURGER, AW, ET AL. Quantitation of differential sensitivity of human-tumor stem cells to anticancer drugs. *N Engl J Med,* 1321–1327, 1978.

14. FREI, E, LAZARUS, H. Predictive tests for cancer chemotherapy. *N Engl J Med,* 298, 1358–1359, 1978.

15. CASCIATO, DA, SCOTT, JL. Acute Leukemia following prolonged cytotoxic agent therapy. *Medicine,* 58, 32–47, 1979.

Changing Concepts of Cancer Biology, Diagnosis and Treatment

ROBERT N. TAUB, MD, PhD

Professor and Chairman, Division of Medical Oncology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia.

Cancer is the number two killer in the United States and will probably account for some 400,000 deaths in 1982. The lung has now achieved the dubious distinction of being the most common site of cancer in men and causes the most deaths. Cancer of the colon and rectum is the second most common cancer in both males and females combined, whereas carcinoma of the breast and uterus predominate in women.

The incidence of most cancers has been rising rather slowly over the past several decades for reasons that are not clear, possibly because of increasing contamination of our environment by chemical carcinogens, air pollution, and prescription drugs. In males lung cancer has dwarfed the incidence of most of the other tumors; even in females there is an ominous recent sharp angling of the curve upward. Carcinoma of the stomach and carcinoma of the cervix have markedly declined during the past several years, but the reason for this is unclear. Perhaps the decline may be related to some dietary factor which has been eliminated due to better techniques for preserving or preparing meat.

It is useful to examine the anticipated five-year cancer survival rates for specific sites taken from the Surveillance Epidemiology End Results Group of the National Cancer Institute. Many localized cancers, particulary those of the bladder, breast, colon, larynx, prostate and uterus, show prolonged survival times. The notable exception is the lung with a five-year survival of only 23%, even if the tumor is localized at the time of surgery. The American Cancer Society purports to indicate that this means tumors should be detected earlier. An alternative explanation is that those tumors which remain localized are biologically less malignant and grow more slowly, and therefore have a greater likelihood of being found at a time when they have not yet spread.

What is not emphasized is that for prostatic neoplasms and lung cancer, probably 80–85% of the tumors are disseminated when first discovered, so that the localized cancers are in the distinct minority. Once a tumor has been disseminated, the chances for prolonging survival are greatly diminished.

During the past five years there have been no substantially new modalities of therapy. In some areas our surgical techniques are already extremely refined while in other areas they continue to evolve, as in the currently expanding use of microsurgery in pituitary, pineal, ocular, and laryngeal tumors. There has been a proliferation of endoscopists, and it is now a rare endobronchial, colonic, or jejunal lesion that manages to escape direct visual inspection through the endoscope before it is removed.

Substantial advances have been made in diagnostic radiology, particularly in the areas of CT scanning and ultrasound. Radiotherapeutic techniques have gradually evolved as well. Treatment planning is better because of newer computer-simulated models. The high-voltage linear accelerator and the use of newer heavy particles, such as the neutron and photon beams, have also given a higher therapeutic index in specific problems.

The cumulative impact of these refine-

ments in surgery, radiology, and chemotherapy has been substantial. For example, in radiotherapy there has been great improvement in survival for those who have tumors that are both radiosensitive and tend to be localized. There is little question that we have markedly improved the therapeutic index in retinoblastoma, testicular carcinoma, Hodgkin disease, and have improved the situation in head and neck cancer, as well as prostate, bladder, ovary, and tonsil cancer.

More striking is that a number of cancers, particulary congenital trophoblastic tumors, Burkitt lymphoma, testicular neoplasms, Wilms tumor, and neuroblastoma are now being cured routinely by chemotherapy. Hodgkin disease has been heavily affected by appropriately used radiation therapy and chemotherapy, sometimes in combination. Survival of patients with Hodgkin disease in 1979 is probably greater than 50% for all tumors. Chemotherapy is also generally agreed to be useful for palliation of prostatic carcinoma and breast carcinoma as well as chronic lymphocytic leukemia, lymphosarcoma, and acute myeloblastic leukemia.

We have not changed survival times of patients with the more common solid tumors to any extent despite the progress we have made in controlling the fluid tumors of leukemia and lymphoma. Little progress has been made in prolonging survival of patients with solid organ tumors, particularly those of the lung, colon, and genitourinary tract which are the most common and which far outnumber leukemias and lymphomas. Nevertheless, a great deal of progress has been made during the past decade.

We have learned much about the biological behavior of human tumors, some from animal experimentation and some from carefully designed cooperative clinical trials. There are two important concepts which have had considerable impact: first, the concept of micrometastases and their relationship to tumor burden, particularly in breast cancer; and second, differences in biologic aggressiveness among histologically-similar types of cancer as exemplified by Hodgkin disease.

With respect to the concept of total tumor burden and micrometastases, it should first be stressed that all tumors, when discovered, are actually in a fairly late stage of their growth. If we assume that a tumor begins as a single cell and continues doubling and growing exponentially, it has already divided approximately 30 times to reach a size of about 10^8 or 10^9 cells and a weight of about one gram. A one-cm tumor nodule is probably at the limit of detection either by palpation or x-ray.

Treatment may accomplish any of several goals. An effective treatment may shrink the tumor drastically, perhaps by a factor of a thousand, but unless every cell is destroyed, it is almost certain that the tumor will recur. If the recurrent tumor tends to follow the same kinetics as the earlier tumor, its rate of growth will be the same. This is usually the case except in the case of metastatic tumors; such tumors usually grow faster. In general, the more substantial the response, the longer the survival.

In some instances effective treatment, such as hormonal therapy, may drive the tumor into a state of dormancy or quiescence, so that its rate of growth is changed, but at some later point when it resumes autonomous growth, it will again grow at a rate similar to the rate it exhibited initially or even faster.

Many chemotherapists have spoken of eradication of the last tumor cell. We now know that this is somewhat naive and may perhaps apply to one or two tumors in which most all the cells are actively growing and are susceptible to a chemotherapeutic agent. In the most common solid tumors such as those of the lung, breast, and colon, only a portion of the cells are in cycle and are susceptible to chemotherapy at any one time.

It is likely that many tumors continually shed cells into the circulation, and the cells that are shed must be counted in the total tumor burden. There was an experiment which was performed in mice in which an implanted mammary carcinoma was allowed to grow to the size of 700 mg. At that time surgery was performed, and all visible tumor was excised. Nevertheless, it was clear that there must have been micrometastases at sites distant from the resection because with large tumors essentially no mice remained tumor free one month after surgery.

There is a striking parallelism between this experiment and a similar study performed in humans where the tumor burden was simply measured by the number of positive lymph nodes found during surgery in patients with breast carcinoma. As the number of positive nodes increased, the ten-year survival of these patients fell drastically. A number of surgeons claim that

patients with higher numbers of positive lymph nodes do poorly because the nodes act as a secondary focus of disease and that more extensive operations should be performed.

If this thesis were correct, then there should be clearly demonstrable differences between patients that had different types of operations. The newer operation that is now being performed is a simple or total mastectomy in which just the breast is removed, but the contents of the axilla are not taken (they may be biopsied but are not removed), and the pectoralis muscle is also preserved. This is to be compared with a standard radical mastectomy in which the entire contents of the axilla are removed together with the pectoralis muscle, leaving only the intercostal muscles and the ribs after mastectomy.

After five years the National Surgical Adjuvant Breast Protocol Groups have shown no difference in survival among almost 1,000 patients who underwent different types of mastectomy. This would affirm that the reason for failure of breast carcinoma treatment is due to distant metastases which are not visible at the time of surgery. This concept has had an enormous impact on the area of breast cancer because it has led to trials of adjuvant chemotherapy which have, in fact, greatly improved survival where surgery could not.

In Hogkin disease we have a similar situation but with one additional complicating factor. First, we do know that in Hodgkin disease the total body burden of the disease does bear a close relationship to prognosis. Early in the treatment of Hodgkin disease, many of the observers at Stanford and other institutions concluded that most Hodgkin disease spread by contiguity and that the disease essentially could be cured if radiotherapy could be applied to all the involved fields plus an additional margin of safety around the field. Thus, Stage I could be treated by radiotherapy to the axilla and the mediastinum.

An additional important prognostic factor in Hodgkin disease is the histologic type of the disease. Four current histologic classifications are recognized: lymphocytic predominance, nodular sclerosis, mixed cellularity, and lymphoid depletion. In this progression the last type has the most Reed-Sternberg cells, the least lymphocytes, and the worst prognosis, no matter what the stage. Each of these histologic presentations is closely associated with a specific stage of the disease; for example, lymphoid depletion is extremely rare in Stage I and is most found in Stage III or IV. On the other hand, lymphocytic predominance is usually found as Stage I or Stage II. Although there is some overlap between histologic patterns of the disease, in the main the histologic patterns tend to persist for long periods of time.

It is beginning to appear that Hodgkin disease may consist of at least four separate clinical entities, each of which pursues a different course and for which different management strategies are indicated. For Hodgkin sarcoma, which tends to disseminate rapidly and probably does not spread by contiguity, localized radiotherapy would be useless and systemic chemotherapy would be the more effective agent. Similarly, for lymphocytic predominance, chemotherapy would probably represent too much treatment. An important corollary has been that the presence of systemic symptoms indicates that the disease is aggressive and probably will also require systemic treatment. Thus, even if the disease is Stage II during intensive investigation but systemic symptoms are present, the recurrence rate after radiotherapy only is high so that chemotherapy should be considered even at that early stage.

There are other examples of tumors of different biologic aggressiveness. It is easy to recall the difference in aggressiveness, growth rate and prognosis in patients with estrogen-receptor positive and estrogen-receptor negative breast cancer. In malignant melanoma as well, it has become apparent that certain types of melanoma, particularly the lentigo maligna or the superficial spreading melanoma, are much less virulent than the nodular melanoma. This undoubtedly will be important at a later time in treatment, but as yet no effective treatment regimen has been designed for any of these stages.

Another important topic for which great interest has been generated during the past decade is that of the possibility of immunotherapy, that is to say, that of immunizing the patient against his own tumor. Unfortunately, this treatment will also have to await the future because there is no firm evidence that immunizing patients with their own tumor in ány way has altered survival or produced regression of the disease on its own. When used in combination with chemotherapy, most controlled studies have not

indicated that there is any additional benefit of adding immunotherapy, although the work is not yet completed. One of the important dividends of immunotherapeutic research has been the notion that there are certain antigens on the surfaces of tumor cells which may be important in diagnosis and detection.

The carcinoembryonic antigen (CEA) is a specific antigen which is represented on the surface of colonic tumors and also on the surface of the fetal colon as well. The tumor sheds CEA into the serum, and this can be detected by radioimmunoassay. Whereas CEA levels have not been found to be particularly useful in the detection and screening of colonic carcinoma, they have been valuable for following the course of the patient after surgery. Typically, normal patients do not have CEA levels above five nanograms per ml; colon cancer patients may have much higher levels. If resection is successful and complete, the levels fall rapidly after operation. In 30–40% of cases, the CEA rises several months before recurrence is clinically detectable.

In acute myeloblastic leukemia we have been carrying out similar experiments at this institution in conjunction with the University of Toronto, and we have been performing tests on bone marrow of leukemia patients in remission to determine whether we might predict relapse at an earlier time. Some of our data on 43 patients will soon be published in the *New England Journal of Medicine*.

This suggests that tests can be devised which will pick up impending relapse in patients with myeloblastic leukemia approximately four to five months before the tumor appears in the bone marrow. We hope to exploit this fact by applying reinduction chemotherapy at an earlier stage.

Recent Advances in Gastrointestinal Cancer

GALEN L. WAMPLER, MD

Associate Professor of Medicine, Division of Medical Oncology, Department of Medicine, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

INTRODUCTION

Colorectal carcinoma accounts for the majority of all gastrointestinal cancers and is the second leading site of cancer, excluding skin cancers, in overall incidence in the United States.[1] Cancer of the stomach, although decreasing in frequency, is still an important cause of morbidity and mortality. Unfortunately, data from large numbers of patients such as can be found in Cancer Patient Survival Report No. 5 show only very modest increases in survival for patients with these diseases in recent years.[2]

Gastric Carcinoma

Most patients who develop gastric cancer have regional or distant disease at diagnosis. The presence of regional nodal involvement is almost synonymous with incurability since virtually all these patients are either non-resectable at the time of operation or rapidly develop systemic recurrences. Any improvement in treatment results would be expected to be produced by chemotherapy or immunotherapy rather than from localized forms of treatment.

Fortunately, gastric carcinoma is relatively responsive to chemotherapeutic treatment, and at least four drugs have now been identified as active in treatment of this condition, namely 5-fluorouracil (5-FU), Adriamycin, mitomycin-C, and semustine (methyl-CCNU). Although semustine is the nitrosourea that has been most extensively used in the chemotherapy of gastrointestinal neoplasms, it is still an investigational drug and therefore is not always conveniently available. Other nitrosoureas that are on the market are probably similar in activity.

Percentage of response and increase in survival with single-drug therapy have been modest, and for this reason the drugs have been combined into a variety of multiple-drug regimens. Most of the possible two and three-drug combinations of the four active drugs have been tried.

Table 1 shows response rates and survival figures for some of the most extensively tested combinations. The combination of 5-FU and semustine was one of the first advocated as being superior to 5-FU alone in the treatment of gastric carcinoma. More recently 5-FU plus Adriamycin plus mitomycin-C (FAM) combinations have become more popular. The FAM regimen was initially reported to have a 50% response rate in gastric carcinoma. The most recent update of over 60 patients indicates that the response rate is holding at approximately 43%.[3]

The FAM regimen (Table 2) is a well-tolerated treatment which gives partial or complete responses in about one half of the patients and benefits other patients by stabilizing the disease, resulting in prolonged survival for the population of treated patients. Quality of survival for many is good, and it is not uncommon to see responses lasting for over one year.

One problem with the treatment is cumulative marrow toxicity which is attributed to the mitomycin-C in the regimen. This tends to limit the treatment that can be given after the first few cycles. The cycles of treatment are similar to other day-1, day-8 treatments given every eight weeks.

Other combinations of these drugs which utilize different doses and regimens have also been tried. Two of these used at the Sloan Kettering Institute known as MIFA I and MIFA II confirm that these drugs in combination are effec-

TABLE 1
Combinations Used in Treatment of Gastric Carcinoma

	Response Rate	Med. Survival Weeks
5-FLUOROURACIL + Semustine	9–45%	17–25
5-FLUOROURACIL + ADRIAMYCIN + MITOMYCIN-C	21–43%	24–34
5-FLUOROURACIL + ADRIAMYCIN + Semustine	36%	22–30
5-FLUOROURACIL + MITOMYCIN-C	—	17
ADRIAMYCIN + MITOMYCIN-C	—	—

tive in the treatment of gastric cancer.[4] Table 1 indicates treatment results of these and other combination treatments for gastric cancer. The median survival of patients with untreated advanced gastric carcinoma is four months or about 17 weeks from diagnosis. Since the figures in Table 1 show the survival in weeks from the time of treatment rather than diagnosis for the entire population of treated patients, not just the responders, one can see that a doubling of the survival time for the better combination is achievable.

Dr Charles Moertel from the Mayo Clinic has recently analyzed data combined from several cooperative groups. Using a statistical model, he concluded that 5-FU and Adriamycin contribute most to the treatment of gastric cancer.[5] This is a combination that has not received extensive use, and the projected value of the treatment needs confirmation in a large clinical trial.

Colorectal Carcinoma

Although there have been a number of attempts to improve results in treatment of colorectal cancer, most of these have been futile or have achieved only very modest success. The surgical treatment of colorectal cancer has been standard for several decades, and although some recent studies indicate that preoperative and postoperative radiation therapy given adjuvantly in high-risk patients would be beneficial, particularly in patients with carcinoma of the rectum, these suggestions have not met with widespread acceptance.

Five-fluorouracil has been a standard treatment for colorectal cancer for 20 years, and one might summarize the clinical experience of a number of investigators' attempts to improve results by manipulating the 5-FU dose, schedule, or route of administration by simply stating that no schedule of treatment has been definitely shown to be superior to any other.[6] The most common schedules used have been daily intravenous treatments for five days repeated at five-week intervals or one intravenous treatment administered weekly.

Administered orally, 5-FU gives response rates similar to the intravenous treatments of the drug. However, Moertel[7] has reported that the duration of response is shorter with the oral form of treatment. Absorption is erratic, averaging about 50%. Because of these facts and because no oral form of treatment has been marketed, use of this drug by this route of administration has not gained wide acceptance.

Response rates with 5-FU in colorectal carcinoma average approximately 20%. Two forms of therapy which have a response rate above 10% are the nitrosoureas and mitomycin-C. Other drugs have either had limited use in colorectal cancer or have given response rates of 10% or less, leaving only a few drugs that have a significant response rate in this disease.

A number of combinations have been devised for the treatment of colorectal carcinoma, the more extensively tested combinations being: 5-FU with semustine, mitomycin-C or hydroxyurea; 5-FU plus semustine plus vincristine; and 5-FU plus semustine plus dacarbazine. Response rates for the combinations were initially

TABLE 2
FAM Regimen

Day 1	Day 8	Day 29	Day 36
F	F	F	F
A		A	
M			

F = 5-Fluorouracil	600 mg/M^2
A = Adriamycin	30 mg/M^2
M = Mitomycin-C	10 mg/M^2

Cycles of treatment are repeated every eight weeks.

reported to exceed the results of 5-FU alone. The combination of 5-FU, semustine and vincristine has been said to have response rates in the range of 35 to 40% by at least three different groups.[8,9,10] However, as additional studies and survival data are reported, the superiority of this combination over 5-FU alone has not been confirmed.[6]

Median survival for patients after proof of incurability is approximately 30 to 32 weeks with 5-FU alone, and for the combinations the survival has been in the same range. Consequently, the current consensus is that no combination of drugs for the treatment of colorectal carcinoma has proved to be superior to 5-FU alone. At this time other combinations are being tried which, it is hoped, will yield results surpassing those with only 5-FU.

There is controversy regarding whether or not 5-FU alone increases survival in patients with colorectal carcinoma. To my knowledge, no prospective randomized trials have been done comparing 5-FU with no treatment in patients with advanced disease. Used many years ago for the treatment of advanced colorectal cancer, 5-FU was shown to yield responses and was felt to be beneficial, not only in achieving these responses but also in extending the life of the patient. No one has since been willing to compare it to no treatment.

One can easily demonstrate that 5-FU responders live longer than non-responders. Additionally, retrospective analysis indicates that 5-FU produces a modest increase in median survival in a population of treated patients. Moertel's own data[11] demonstrated that 5-FU treated patients live longer throughout the entire survival curve than matched historical controls. This difference was discounted by Moertel who stated that there is no evidence showing that 5-FU prolongs survival, attributing the difference to patient selection. This is only an opinion, and different interpretations are possible.

A number of surgical adjuvant trials have been conducted in patients with colon and rectal carcinomas. One of the earliest studies utilized thiotepa or fluorodeoxyuridine (FUdR) after surgery. This particular study showed no effect. However, it is of interest that these patients, followed over a decade, had no increase in carcinogenicity or other late toxicity which could be ascribed to those treatments.[12] More recently a number of studies have been done utilizing 5-FU in adjuvant treatment. In the non-randomized studies using historical controls, 5-FU was reported to produce a beneficial effect[13,14]; in the randomized studies the 5-FU, in all cases, produced a slight prolongation of disease-free interval and survival in the treated group.[15–19] Initially, the difference was judged not to be statistically significant; however, a recent statistical analysis using cumulative results involving larger patient numbers resulted in the conclusion that there is a statistically significant improvement, at least for some subsets of 5-FU-treated patients in the adjuvant setting. Results of these studies are still pending.

In an article in the *Annals of Internal Medicine*,[20] Drs Weiss and Devita stated that at the present time whether or not a patient receives adjuvant chemotherapy for colorectal carcinoma is a decision that needs to be individualized for each patient. This is primarily because the results of 5-FU have been marginal at best, and the potential benefits of therapy may be overridden by a variety of other factors: disease stage (patients with Duke's B2 or C stage lesions, *eg*, extension through the muscular layer and/or involved nodes are customarily treated); age of the patient; histologic grade of the tumor; economic factors; and convenience of travel to the treatment center for the patient. Following a trial of adjuvant treatment, the decision to continue treatment should be based on the patient's tolerance tempered by the knowledge of limited survival benefit.

Other Gastrointestinal Tumors

There are three uncommon types of gastrointestinal malignancies, all of which show significant response rates to treatment with chemotherapy.

Leiomyosarcomas are found in the stomach and in the bowel. Recurrent or metastatic tumors respond to treatment with Adriamycin in approximately 30% of cases, and if combined with dacarbazine, the response rate may be 10% higher. The treatment for metastatic leiomyosarcomas of the bowel is the same as for other metastatic sarcomas.

Lymphomas also occur in the gastrointestinal tract, and although their natural history may be somewhat different from those originating elsewhere, the chemotherapeutic treatment is basically similar. Where the histology predicts a favorable outcome, treatment would probably

consist of cyclophosphamide plus vincristine plus prednisone (COP) therapy and the unfavorable ones treated in addition with Adriamycin and possibly with Bleomycin.

Carcinoid tumors are also responsive to chemotherapeutic treatment. About one third of these patients with advanced disease show objective responses to treatments with 5-FU and streptozotocin in combination. More recently Adriamycin has been used as a single agent. Treatment for this condition is still very much in a stage of evolution.

Other Advances

The biologic marker known as carcinoembryonic antigen (CEA) which has been developed for clinical use in the last decade, has contributed materially to our ability to stage and follow patients with colorectal carcinoma. The initial hope was that the test would be useful as a diagnostic and screening tool. It has not proved to be very useful for this purpose. However, it has been found to be beneficial as a prognostic indicator. Patients with high levels of CEA prior to surgery will not do as well as patients with normal levels. It can also be utilized to assess adequacy of treatment or to evaluate disease recurrence and treatment response. It has been suggested that CEA-producing tumors are inherently more likely to metastasize and are less controllable by the body's immune processes. This biological difference, if confirmed, will undoubtedly influence future treatment strategies.

Table 3 presents data taken from a study where 2,372 patients of an unselected population were screened for malignancy using CEA values.[21] Seventy-three of these patients were found to have elevated CEA levels above 5 ng/ml. Workup of these 73 patients resulted in the finding of malignancy in only 11 patients. Nine had a CEA-related malignancy and two had an incidental malignancy. The false-positive rate, therefore, was calculated at 87%.

TABLE 3
Use of CEA in Screening an Unselected Population[21]
2372 people followed 5 years
87% False Positive 64% False Negative

	CEA LEVEL <5 ng/ml	CEA LEVEL ≥5 ng/ml	
Developed a CEA related Cancer	16	11*	25
Never developed Cancer	2000+	62	
			73

(3% of total population)

* two others were found to have incidental cancers not related to CEA evaluation.

More disturbing than even the high false-positive rate was the fact that 16 patients who were CEA-negative developed a CEA-associated cancer during the follow-up period for a false-negative rate of 64%. Only 3% of the 2,372 patients had elevated CEA levels which is consistent with the fact that 95% of a normal population are known to have CEA below 2.5 ng/ml. (In this population, 97% had the CEA level below 5 ng/ml.) The low incidence of cancer in this population of 2,372 resulted in the high false-negative percentage. CEA testing may play a role in screening certain high-risk populations, but it is not suitable as a screening mechanism for carcinoma of the colon in unselected populations.

It was originally thought that CEA would be specific for colon carcinoma since the antigen was obtained from fetal colonic tissue. However, it was soon found that it is non-specific for colon carcinoma, being elevated in a variety of other malignancies including breast, lung, pancreas, stomach and bladder carcinomas, and in other malignancies. CEA is also elevated in patients with liver disease, pancreatic cysts, gastrointestinal polyps and other benign conditions. The CEA is not specific for a particular primary site and is not even as specific as one would like for malignancy.

With the understanding of certain characteristics of biologic markers shown in Table 4, CEA tests can be used quite advantageously for a number of purposes. In general, biologic markers are non-specific for histologic types of neoplasms and often are not even specific for malignancy. The specificity and sensitivity tend to be inversely related. By developing a more sensitive assay, more positive results will be obtained in patients with non-malignant conditions or with tumor types other than those anticipated. In contrast, if normal levels are drawn at a higher concentration, the test is more specific. For example, most patients with CEA over 10 ng/ml will have a malignancy.[22] The percentage of patients with positive markers increases with the stage of the disease. Reports of CEA elevation in the 90% range are applicable only

TABLE 4
Some Characteristics of Biologic Markers

1. In general biologic markers are non-specific for a histologic type of neoplasm and often are not even specific for malignancy.
2. Sensitivity and specificity tend to be inversely related.
3. The percentage of patients with positive markers increases with stage of disease.
4. Not all patients develop positive markers.
5. Marker status is not a dependent variable in relatipn to staging.

to patients with advanced colorectal carcinoma. The figure is much lower for patients with localized or regional disease only.

Not all patients develop positive markers. Only those patients with certain phenotypic cancer cell expressions will show marker elevation. Other patients having histologically-similar tumors will never be marker positive. Therefore, it is futile to attempt to manipulate a test to give results 100% of the time or to look for new markers that will do this.

The percentage of CEA positivity in patients with colonic cancer was initially reported in excess of 90%. Later the percentage fell, the reason being that initially patients with advanced disease were tested, and in the later series more patients with earlier stages of disease were tested.[23] The percentage of CEA elevation directly correlates with the stage of disease; however, it is not a dependent variable, meaning that the distribution of CEA positives in patients of various stages has a tendency toward randomness. In general, CEA and other biologic markers are not dependent variables in relation to the stage of disease or any other known prognostic factor. This means that prognostication is improved by considering marker values along with stage, grade of tumor and other standard prognostic indicators.

CEA is also useful in following colorectal patients for recurrence. The majority of patients who are found to have recurrences will have shown at least one CEA elevation greater than 2.5 ng/ml more than three months before documentation of recurrence. One study[24] showed 54% of the patients having this marker positive (>2.5 ng/ml) more than three months prior to the documentation of recurrence. If a higher positive value (5 ng/ml) is used, 41% will have an elevation three months before clinical tumor recurrence. An additional number of patients will have markers positive for three months or less prior to recurrence. The percentage of patients who show elevated CEA prior to recurrence of colon cancer is higher than in rectal cancer. (Table 5).

In colon cancer only 14% are never elevated prior to documentation of recurrence compared to 32% for rectal cancer. While this looks quite good as a tool for predicting recurrences, it has to be tempered by the fact that matched controls also have a high percentage of at least one elevated CEA value. The matched controls were patients with the same age, the same disease, and treatment, who had not had a recurrence during periods of equal follow-up. Some of these patients will eventually turn out to have a recurrence because it is known that the CEA can be elevated for as long as several years prior to recurrence. Some of these patients have random increases in CEA value; others have benign causes of the elevation.

It is known that patients who receive blood products at the time of their surgery sometimes develop CEA elevations that plateau and later decrease[25] secondary to hepatitis or undetermined factors in the absence of acute or chronic liver disease. The problem in following these patients is to separate those who have random elevations or benign conditions from those who have a recurrence of malignancy. In order to distinguish those with random elevations, a CEA nomogram has been developed to indicate when values are statistically increased. Nomograms are published in the literature,[26,27] but to be valid, each laboratory should construct its own based on the precision of its test. While the nomogram is useful in differentiating patients who have a random increase from those with a true increase in CEA levels, repeating the value several times helps in making this differentiation.

It is important to make a diagnosis of recurrence earlier using CEA elevations. Some of these patients may be candidates for second surgery; others will be candidates for radiation therapy or chemotherapy. In considering possible patients for second surgery, it is necessary to separate those patients who are going to have an operable malignancy from those who have random fluctuation of the CEA, benign conditions, and inoperable lesions. Using the nomogram, one can distinguish most random fluctuations. Benign conditions tend to be

TABLE 5
Percentage of Patients With Established Tumor Recurrence Who Exhibit CEA Elevations [24]

Primary Tumor Site	>2.5 ng/ml >3 mos before recurrence	>5 ng/ml >3 mos before recurrence	>2.5 ng/ml <3 mos before recurrence	>5 ng/ml <3 mos before recurrence	Never elevated
COLON	58	45	28	26	14
RECTUM	42	31	26	32	32
COMBINED	54	41	29	28	17

nomogram positive as are both operable and inoperable malignancies. The operable malignancies and random fluctuations would not be expected to have elevated liver enzymes. The degree of CEA elevation helps to discern the operable and inoperable malignancies. High elevations correlate with metastatic disease and more specifically with liver metastases.

To determine operable cases one looks for patients with minimal elevations of CEA. In one series the mean elevation in the operable patients was 6.5 ng/ml compared to 15.5 ng/ml in those who had inoperable malignancy.[28] Additional information can be gained by looking at the character of the rise. If a benign condition exists, the CEA tends to plateau at levels usually less than 10 ng/ml. For any type of malignant condition, an exponential rise occurs; the slope of the rise for those who are operable is less than that for the inoperable ones. The value is probably in the range of 0.5 ng/ml/mo or less for operable cancers and >1 ng/ml/mo for inoperable patients.[29]

A factor to be considered in the decision for reoperability is the interval between surgery and observed CEA elevation. The benign causes of the CEA elevations occur earlier after surgery than the operable malignancies.[27] Any CEA elevations that occur early are more likely to be associated with inoperability. If they are caused by tumor, they probably are rising at a more rapid rate than those that occur later. Patients whose CEA elevations occur more than five months after surgery are more likely to be eligible for reexploration. These factors are summarized in Table 6.

It is important to stress that the decision regarding reoperation is not based on just the CEA level. A careful determination must be made that the patient does not have clinical metastatic disease by obtaining a chest x-ray, liver scan, serum chemistries, and other appropriate tests such as sonography, abdominal CT scan, and liver biopsy if other tests are negative. Careful monitoring and testing will exclude five sixths of the patients for consideration for

TABLE 6
Differential Diagnosis of CEA Elevation

Cause of CEA Elevation	Nomogram	Liver Enzymes	Degree of Elevation	Character of Rise	Time of Occurrence Post-Resection
Random Fluctuation	− or ±	−	Depends on Baseline Value	Not Verifiable	Random
Benign Condition	+	Often +	Usually <10ng/ml	Non Exponential (Plateau)	Median Time < 5 mo.
Operable Malignancy	+	−	Mean 6.5 ng/ml	Exponential Slope <1ng/ml/mo	Median Time > 5 mo.
Inoperable Malignancy	++	Often +	mean 15.5ng/ml	Exponential Slope > 1ng/ml/mo	Median Time > 5 mo.

"second-look" surgery. Of the remaining one sixth, the resectability rate may be as high as 30%.[30] Increasing the percentage of patients operated on will decrease the resectability percentage. The cure rate for the patients who are resected a second time is not known.

A practical strategy for following patients with colorectal cancer with CEA assays is presented. Preoperative levels should be obtained for establishing a base line and serve as a prognostic indicator. The test should be repeated postoperatively. Two weeks after surgery is both convenient and appropriate; however, if the CEA level has not returned to normal, the test should be repeated.

Apparently not all CEA values return to normal promptly. If they remain elevated, it is important to establish a base line for nomogram analysis. Subsequently, values are obtained every two months for the early detection of recurrence. After one year the test could be run less frequently. If a significant elevation is encountered outside the normal nomogram range, the test is repeated serially, two or three times, to verify elevation and determine, if possible, the character of the rise. Concurrently, the patient is evaluated carefully for metastatic disease. Selected patients may be candidates for surgery.

In patients who have developed metastatic disease, CEA can be used for evaluation of chemotherapeutic or radiotherapeutic response. The CEA appears to be more correlated with tumor burden if its value is below 100 ng/ml. While this correlation is sometimes erratic, it is the most valuable tool available in patients who do not have measurable disease.

CONCLUSION

Chemotherapy has produced significant improvement in treatment results for gastric carcinoma, but to date only minimal improvement has been achieved for colorectal carcinoma. Earlier application of radiation therapy, specifically preoperative and postoperative radiation therapy, particularly for patients with carcinoma of the rectum, is sufficiently attractive for further study.

The primary area of improvement for patients with colorectal carcinoma has been in our ability to assess the status of the disease and in our beginning understanding of the biologic differences in patients with the disease. Ultrasonography and CT scanning are relatively new procedures whose effect on the overall problem remains to be assessed. Carcinoembryonic antigen testing is clearly an important advance, and there is every indication that other useful markers will be developed.

The net effect of all these developments is the increased ability to select patients accurately for given treatments and to follow treatment results more precisely. It is known from previous experience that in those diseases in which the assessment of results is difficult, progress has been slow. Therefore, it is anticipated that more rapid improvements in treatments in the coming years will ultimately be reflected in the overall survival statistics of these diseases.

REFERENCES

1. Cancer Facts and Figures. American Cancer Society, 1980.

2. Axtell LM, Asirc AJ, Myers MH: Cancer Patient Survival Report Number 5. DHEW Publication no. (NIH) 77-992. National Cancer Institute, Bethesda, MD, 1976.

3. McDonald JS, Schein PS, Woolley PV, et al: Five-fluorouracil (5-FU), Mitomycin-C (MMC) and Adriamycin (ADR) FAM Combination Chemotherapy Results in 61 Patients with Advanced Gastric Cancer. *Proceedings of the American Society of Clinical Oncology* 20:396, 1979.

4. Schauer P, Magill GB, Howard J, et al: Combination Chemotherapy of Gastric CA with MIFA II or with AAFC-CPPD. *Proceedings of the American Society of Clinical Oncology* 20:335, 1979.

5. Moertel CG, O'Connell MJ, Lavin PT: Chemotherapy of Gastric Cancer. *Proceedings of the American Association for Cancer Research* 20:288, 1979.

6. Moertel CG: Current concepts in cancer chemotherapy of gastrointestinal cancer. *N Engl J Med* 229:1049–1952, 1978.

7. Hahn RG, Moertel CG, Schutt AJ, et al: A double-blind comparison of intensive course 5-fluorouracil by oral versus intravenous route in the treatment of colorectal carcinoma. *Cancer* 35:1031–1035, 1975.

8. Moertel CG, Schutt AJ, Hahn RG, Reitmeier RJ: Therapy of advanced colorectal cancer with a combination of 5-fluorouracil, methyl-1, 3-cis (2-chloroethyl)-1-nitrosourea, and vincristine. *JNCI* 54:69–71, 1975.

9. FALKSON G, FALKSON HC: Fluorouracil, methyl-CCNU, and vincristine in cancer of the colon. *Cancer* 38:1468–1470, 1976.

10. MACDONALD JS, KISNER DF, SMYTHE T, ET AL: Five-fluorouracil (5-FU), methyl-CCNU and vincristine in the treatment of advanced colorectal cancer: Phase II study utilizing weekly 5-FU. *Cancer Treat Rep* 60:1597–1600, 1976.

11. MOERTEL CG: Clinical management of advanced gastrointestinal cancer. *Cancer* 36:675–682, 1975.

12. GREENE MH, BOICE JD, KEEHN RJ, ET AL: Late Effects of Low Dose Adjuvant Chemotherapy in Colorectal Cancer. *Proceedings of the American Society of Clinical Oncology* 20:413, 1979.

13. LI MC, ROSS ST: Chemoprophylaxis for patients with colorectal cancer: Prospective study with five-year follow-up. *JAMA* 234:2825–2828, 1976.

14. MAVLIGIT GM, BURGESS MA, SEIBERT GB, ET AL: Prolongation of postoperative disease-free interval and survival in human colorectal cancer by B.C.G. or B.C.G. plus 5-fluorouracil. *Lancet* 1:1248, 1976.

15. LAWRENCE W JR, TERZ JJ, HORSLEY S III: Chemotherapy as an adjuvant to surgery for colorectal cancer. *Ann Surg* 181:616–623, 1975.

16. HIGGINS GA JR, DWIGHT RW, SMITH JV, ET AL: Fluorouracil as an adjuvant to surgery in carcinoma of the colon. *Arch Surg* 102:339–343, 1971.

17. HIGGINS GA JR, HUMPHREY E, JULER GL, ET AL: Adjuvant chemotherapy in the surgical treatment of colorectal cancer. *Cancer* 38:1461–1467, 1976.

18. BLIKHINA NG, GARIN AM, LIPATOU AM: Results of Five Year Observation for Patients Receiving 5-Fluorouracil After Radical Surgery for Carcinoma of the Colon and Rectum. *Proceedings of the Second All-Union Cancer Chemotherapy Conference,* Kiev, September 1974, pp 243–244.

19. GRAGE TB, METTER GE, CORNELL GN, ET AL: The role of 5-fluorouracil as an adjuvant to the surgical treatment of large bowel cancer. *Adjuvant Therapy of Cancer,* Salmon SE, Jones SE (eds). Amsterdam, Elsevier/North Holland, pp 259–263, 1977.

20. WEISS RB, DEVITA VT: Multimodal primary cancer treatment (adjuvant chemotherapy): Current results and future prospects. *Ann Intern Med* 91:251–256, 1979.

21. MACKAY IR: Use of Carcinoembryonic Antigen in Screening an Unselected Population: A Five Year Followup in Clinical Application of Carcinoembryonic Antigen Assay. *Proceedings of a Symposium held in Nice, France,* Oct. 7–9, 1977, vol 439, pp 419–421, Amsterdam, Excerpta Medica International Congress Series, 1978.

22. LOEWENSTEIN MS, ZAMCHECK N: Carcinoembryonic antigen (CEA) levels in benign gastrointestinal disease states. *Cancer* 42(3):1412–1418, 1978.

23. ZAMCHECK N: The present status of CEA in diagnosis, prognosis, and evaluation of therapy. *Cancer* 36:2460–2468, 1975.

24. RAMMING KP, MACINTYRE J, ZAMCHECK N, ET AL: Serum carcinoembryonic antigen (CEA) monitoring of patients at high risk for recurrence following surgery for colorectal carcinoma. *Proceedings of the American Society of Clinical Oncology* 20:329, 1979.

25. GITNICH GL, MOLNAR IG: Carcinoembryonic antigen: Transmission by blood products. *Cancer* 42(3):1568–1573, 1978.

26. MARTIN EW, JAMES KJ, HURTUBISE PE, ET AL: The use of CEA as an early indicator of gastrointestinal tumor recurrence and second-look procedures. *Cancer* 39:440–446, 1977.

27. RITTGERS RA, STEELE G JR, ZAMCHECK N, ET AL: Transient carcinoembryonic antigen (CEA) elevations following resection of colorectal cancer: A limitation in the use of serial CEA levels as an indicator for second-look surgery. *JNCI* 61:315–318, 1978.

28. MINTON JP, MARTIN EW JR: The use of serial CEA determinations to predict recurrence of colon cancer and when to do a second-look operation. *Cancer* 42:1422–1427, 1978.

29. STAAB HJ, ANDEVER A, STUMPF E, ET AL: Slope analysis of the postoperative CEA time course and its possible application as an aid in diagnosis of disease progression in gastrointestinal cancer. *Am J Surg* 136:322–327, 1978.

30. WILSON RE, PERENCEVICH NP, OLSON R, ET AL: Colorectal adenocarcinoma: Patterns of metastases after curative resection and the role of serial CEA measurements in their management. *Eur Surg Res* 10:115–116, 1978.

Breast Cancer: An Update

WADE K. SMITH, MD

Associate Professor of Medicine, Division of Medical Oncology, Department of Medicine, and the MCV/VCU Cancer Center, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

Breast cancer comprises approximately 13.9% of all cases of malignancy in both sexes and 19% in women, in whom it is the commonest form of cancer.[1] The American Cancer Society estimates that 110,000 women developed breast cancer in 1981, and some 37,100 deaths from the disease occurred.[2] The five-year survival rate has been improving over the past 40 years as shown in Table 1[1], but patients remain in risk of recurrence indefinitely, and survival for ten years is generally accepted as the minimal time period necessary to establish the validity of new therapies.

Data from the first study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) are shown in Table 2 and indicate that the majority of women with breast cancer ultimately succumb to the disease.[3] Thus, although only 10% of cases present with metastatic disease (an additional 5% predictably have very rapid progression: inflammatory carcinoma, extensive local or regional disease), over half of those undergoing mastectomy will develop recurrence within ten years.

The identification of women with either adverse or favorable prognostic features modifies these figures considerably. Among the important favorable variables are: attainment of menopausal status for at least five years; increasing age; primary tumors two cm in diameter or less; absence of regional node involvement; estrogen and progesterone receptor positivity and, for estrogen receptors at least, absolute amount of receptor; delay between initial presentation and recurrence; skin or nodal local recurrence as opposed to visceral metastasis; and perhaps most important, an overall less aggressive biological character of the tumor.

Adverse prognostic features include: a clinical picture of inflammatory carcinoma; concurrent pregnancy; liver metastasis; multiple visceral metastases at presentation; brain, meningeal, epidural involvement, or spinal cord compression secondary to vertebral collapse; lymphangitic pulmonary spread; absence of estrogen and, possibly, progesterone receptor; failure of previous therapy for systemic disease; and inability to withstand the toxicities associated with chemotherapy or hormonal therapy. An excellent review of all phases of breast cancer has recently been published.[5]

I intend to concentrate on four areas in greater detail: 1) the usefulness of receptor assays in predicting the response to therapy; 2) chemotherapy of advanced metastatic disease; 3) adjuvant chemotherapy following surgery; 4) the usefulness of antiestrogens in hormonally-responsive disease.

Receptor Assays

Steroid hormones are known to act by crossing the cell membrane where they bind to specific cytoplasmic receptors. The receptor-steroid complex is activated and translocates to the nucleus where it interacts with chromatin.

Supported in part by Grant Number CA 25045 awarded by the National Cancer Institute and CA 15492 awarded through the National Bladder Cancer Project by the National Cancer Institute, DHEW,

Correspondence and reprint requests to Dr Wade K. Smith, Box 162, Medical College of Virginia, Richmond, Virginia 23298.

TABLE 1
Five-Year Survival Rates in Breast Cancer

1940–1949	53%
1953–1959	60%
1960–1964	62%
1965–1969	64%

(*Note:* Adapted from Cutler SJ, Myers, MH, Green SB: Trends in survival rates of patients with cancer. *N Engl J Med* 293: 122–124, 1975.) **(By Permission)**

As a result of this interaction, RNA synthesis is increased and new proteins are synthesized.[6] It now seems that the appearance of progesterone receptors in breast tumors is the result of estrogen stimulation and is a measure of hormonal responsiveness (Table 3).[7]

The presence of estrogen receptor (ER) is an important determinant of prognosis independent of the effects of age, nodal involvement and primary lesion size (Table 4). The ER level is less in the tumors of younger women and is less in primary as opposed to metastatic tumor (Table 5).[7]

Estrogen receptor positivity successfully predicts objective responses to hormonal therapy (Table 6) to the extent that only ER+ patients should be treated initially with ablation or hormone administration.[7,8] It is of interest that the perimenopausal patient, classically *not* responsive to hormonal therapy, tends to have lower ER positivity than either the premenopausal or postmenopausal (five years or more) patient. Clearly the traditional treatment decision based on premenopausal or postmenopausal status alone must be modified to include ER status.

TABLE 2
Results of Surgical Treatment Alone

	Ten-Year Treatment Failure Rate	Ten-Year Survival
Negative nodes	24%	65%
Positive nodes:		
1–3	65%	38%
4 or more	86%	13%
All	76%	25%
All patients	50%	46%

(Note: Adapted from the first NSABP Protocol) **(By Permission)**

TABLE 3
Objective Response to Endocrine Therapy

	No. Responding/ No. Evaluable	% Response
Estrogen-Receptor Negative/ Progesterone-Receptor Negative	9/63	14%
Estrogen-Receptor Positive/ Progesterone-Receptor Positive	67/91	74%

(*Note:* Adapted from McGuire WL: Hormone receptors: Their role in predicting prognosis and response to endocrine therapy. *Semin Oncol* 5: 428–433, 1978) **(By Permission)**

Chemotherapy of Advanced Breast Cancer

A large number of chemotherapeutic drugs have been shown to produce objective responses defined as partial and complete responses (Table 7). Table 8 lists a number of the commonly used agents and responses. The early studies of Greenspan and others suggested that combination therapy was considerably more effective, and therefore the initial chemotherapeutic treatment is almost always a combination, most commonly Cytoxan-Methotrexate-5-fluorouracil (CMF). The CMF combination shown in Table 9 is based on an Eastern Cooperative Oncology Group (ECOG) protocol with 49/93 patients responding. Complete responses lasted a median of eight or more months, partial responses four to eight months. Many oncologists, including myself, use less Methotrexate, 30–40 mgm/M^2, and one series

TABLE 4
Estrogen Receptor and the Prognosis for Early Recurrence of Breast Cancer

Category	Recurrence at 18 months (%) Estrogen-Receptor Negative	Estrogen-Receptor Positive
Age:		
Less than 50	34	14
Over 50	35	8
Nodes involved:		
0	12	6.5
1–3	38	12.5
4 or more	62	27.0
Size of primary:		
Less than 2 cm	33	0
Greater than 2 cm	31	14

(*Note:* Adapted from Table 1, McGuire WL: *Semin Oncol* 5: 428, 1978, and Knight WA, et al: *Cancer Res* 37: 4669, 1977.) **(By Permission)**

TABLE 5
Distribution of Estrogen Receptor in Primary and Metastatic Breast Cancer

	Primary Biopsy		Metastatic Biopsy	
Age:	Under 50	50 or over	Under 50	50 or over
ER level:				
Under 3	37%	23%	52%	31%
3–10	20%	15%	14%	16%
11–100	41%	36%	29%	27%
101–2000	2%	20%	5%	20%

(*Note*: Taken from Table 2, McGuire WL: *Semin Oncol* 5: 429, 1978.) **(By Permission)**

showed a 62% response rate with CMF using Methotrexate at 40 mgm/M^2.

There is no doubt that the single most effective drug is doxorubicin hydrochloride (Adriamycin$^{(R)}$) with reported response rates of up to 45%. Combinations using Adriamycin also show a higher response rate than CMF or CMFP (See Table 9), and some oncologists use CAF as the initial treatment. It is, however, desirable to have a combination available for use after the initial treatment fails, and we have tended to reserve Adriamycin for use in relapse, usually combining it with the vinca alkaloid, vincristine.[4] An exception to this sequence is the premenopausal, ER– patient with extensive visceral and bone disease. These women usually have very rapid, progressive disease, and initial treatment with CAF is warranted in an attempt to obtain even a small measure of control of their disease.

An additional consideration is the treatment of the ER+ patient with combined hormonal and chemical therapy. Only some 10–20% of objective responses are complete responses, but patients achieving complete responses tend to have longer remissions and better survival. Moreover, a small number may be curable since the achievement of complete response in large numbers of patients has been associated historically with the development of very long-term survival or cure. Thus attempts to increase the number of patients achieving complete response and to maintain those in complete response for as long as possible are now the subject of intense study.

Legha and his colleagues at the M. D. Anderson Hospital and Tumor Institute recently reported on 116 patients with breast cancer achieving complete remission. A marked improvement in the number in complete response and the duration of complete response was seen in premenopausal patients who underwent

TABLE 6
Objective Response by Therapy and Estrogen Receptor

Therapy	Objective Response/Evaluable Patients		
	ER+ #%	ER– #%	Pre-ER patients (All comers)
Ablative Surgery:			
Adrenalectomy	40/76 (53%)	4/41 (10%)	28%
Oophorectomy	28/43 (65%)	2/74 (3%)	29%
Hypophysectomy	9/14 (64%)	0/12 (0%)	33%
Total	77/133(58%)	6/127(5%)	
Hormonal Therapy:			
Androgens	10/28 (36%)	2/22 (9%)	18%
Estrogens	38/60 (63%)	2/49 (4%)	36%
Glucocorticoid	15/32 (47%)	0/19 (0%)	29%
Total	63/120(53%)	4/90 (4%)	
Antiestrogens:			
Nafoxidine	12/17 (71%)	0/16 (0%)	
Tamoxifen	18/40 (45%)	0/15 (0%)	
Total	30/57 (53%)	0/31 (0%)	33%

(*Note:* Adapted from Table 2, Legha SS et al: *Ann Intern Med* 88: 69, 1978, and Table 4, Carbone PP, Davis TE: *Semin Oncol* 5: 417, 1978.) **(By Permission)**

TABLE 7
Tumor Response

Complete Remission	No clinical evidence of active tumor; no subjective evidence of disease
Complete Response	All measurable disease disappears
Partial Response	50% or greater reduction in measurable tumor in the absence of progression or recurrence of new lesions elsewhere
Stable Disease	Steady state or response less than 50% reduction in measurable tumor. No increase in size of any lesion or appearance of new lesions
Progressive Disease	Occurrence of any new lesion or increase of any measurable lesion > 50%, even in the face of regressing lesions elsewhere

(*Note:* Adapted from Carter SK: The design of clinical trials in cancer therapy (ed. M Staquet) Brussels: Éditions Scientifiques Européennes, 1972.) **(By Permission)**

oophorectomy and received chemotherapy immediately compared to women receiving chemotherapy when disease progression occurred.[9]

An earlier study of adrenalectomy, oophorectomy and chemotherapy by Hoge et al revealed a much higher objective response rate (80%) when compared to chemotherapy or hormonal ablation alone.[10] These and other studies suggest that attempts to increase the number of patients in complete response by combined therapy may be worthwhile. However, such studies remain research protocols, and much longer observation will be necessary to assess their true value.

Adjuvant Chemotherapy

The large number of patients failing to achieve cure following radical mastectomy sug-

TABLE 8
Summary of Single Agents Active Against Advanced Breast Cancer

Drug	No. Evaluable Patients	No. Objective Responses	Response (%)
Alkylating agents:			
Cyclophosphamide	529	182	34
Nitrogen mustard	92	32	35
Phenylalanine mustard	86	20	23
Chlorambucil	54	11	20
Thio-TEPA	162	48	30
Antimetabolites:			
5-Fluorouracil	1263	324	26
Methotrexate	356	120	34
6-Mercaptopurine	45	6	13
Arabinosyl cytosine	64	6	9
Vinca Alkaloids:			
Vincristine	226	47	21
Vinblastine	95	19	20
Antibiotics:			
Actinomycin D	44	5	11
Adriamycin	193	67	35
Bleomycin	8	0	0
Mithramycin	32	5	16
Mitomycin	60	23	38
Miscellaneous agents:			
Hydroxyurea	21	4	19
BCNU	76	16	21
CCNU	155	18	12
Methyl CCNU	33	2	6
Hexamethylmelamine	39	11	28
Imidazole carboxamide	29	2	7
Procarbazine	21	1	5

(*Note*: Compiled by Susan J. Mellette, MD, Professor of Medicine, Medical College of Virginia.)

TABLE 9
Useful Drug Combinations in the Treatment of Breast Cancer

Regimen	Drug Dosage and Schedule	Response Rate (%)
CMFVP	Cyclophosphamide 80 mg/m² p.o. daily	62
	Methotrexate 20 mg/m² i.v. weekly	
	Fluorouracil 500 mg/m²i.v. weekly	
	Vincristine 1.0 mg/m² p.o. daily × 15 (then taper)	
CMF	Cyclophosphamide 100 mg/m² p.o. days 1–14	53
	Methotrexate 60 mg/m² i.v. days 1 & 8	
	5-Fluorouracil 600 mg/m² i.v. days 1 & 8	
	(repeat cycles every 4 weeks)	
CMFP	Cyclophosphamide 100 mg/m² p.o. days 1–14	63
	Methotrexate 60 mg/m² i.v. days 1 & 8	
	5-Fluorouracil 600 mg/m² i.v. days 1 & 8	
	Prednisone 40 mg/m² p.o. days 1–14	
	(repeat cycles every 4 weeks)	
AV	Adriamycin 75 mg/m² i.v. day 1	52
	Vincristine 1.4 mg/m² i.v. day 1 & 8	
	(repeat cycles every 3 weeks)	
CA	Cyclophosphamide 200 mg/m² p.o. days 3–6	74
	Adriamycin 40 mg/m² i.v. day 1	
	(repeat cycles every 3–4 weeks)	
CAF	Cyclophosphamide 100 mg/m² p.o. days 1–14	82
	Adriamycin 30 mg/m² i.v. days 1 & 8	
	Fluorouracil 500 mg/m² i.v. days 1 & 8	
	(repeat cycles every 4 weeks)	
DAV	Dibromodulcitol 150 mg/m² p.o. days 1–10	71
	Adriamycin 45 mg/m² i.v. day 1	
	Vincristine 1.2 mg/m² i.v. day 1	
	(repeat cycles every 4 weeks)	

(*Note*: From Table 3. Carbone PP, Davis TE: *Semin Oncol* 5:417, 1978.) **(By Permission)**

gests that breast cancer is in fact a systemic disease at a very early stage, if not at its onset. There is increasing evidence to support a multicentric origin for many tumors including breast cancer, and it is now apparent that very large numbers of cells are shed systemically by even small cancers. Moreover, surgical failure results in local recurrence in only about 15% of cases, and most of these patients eventually show dissemination at other sites.[4] Adjuvant chemotherapy given after surgery is designed to destroy disseminated tumor cells and increase the likelihood of cure.

Two major groups have studies in progress: the National Surgical Adjuvant Breast Project (NSABP) and the National Tumor Institute in Milan.[11,12,13] The initial NSABP trial used a single drug, L-phenylalanine mustard, and the first Milan study used CMF for 12 cycles. Benefit was seen in premenopausal patients with one to three nodes involved in both series and for four or more nodes in the Milan series. Tables 10A and 10B show data updated to four years as of May 1978 and represent the most recent comparative data. No benefit to premenopausal women without nodal involvement has been demonstrated. The situation for postmenopausal women is less certain at present because the Milan study is reported to show benefit for the woman with four or more nodes who is able to take 85% or more of the scheduled adjuvant chemotherapy.[13] The NSABP data do not show benefit. Therefore adjuvant therapy should be reserved for premenopausal women with one or more positive axillary nodes. To date, a clear-cut advantage for three drugs and for the duration of treatment has not been established, although treatment for six months and 12 months does not appear much different at the present.[14]

Antiestrogens

A number of steroidal and non-steroidal compounds have antiestrogenic effects. Most clinical trials have employed the nonsteroidal compounds nafoxidine and tamoxifen. The lat-

TABLE 10

A. Comparison of NSABP/Milan Data -Control Patients-

Age/ Menopause	Positive Nodes	% Disease Free at Four Years	
		NSABP	Milan
All Pts.	All	51	47
All Pts.	1–3	63	54
All Pts.	4	40	32
49/Pre-	All	43	41
50/Post-	All	56	52
49/Pre-	1–3	54	49
49/Pre-	4	35	23
50/Post-	1–3	67	58
50/Post-	4	43	42

5/78

B. Comparison of NSABP/Milan Data -Treated Patients-

Age/ Menopause	Positive Nodes	% Disease Free at Four Years	
		NSABP	Milan
All Pts.	All	59	66
All Pts.	1–3	74	74
All Pts.	4	40	49
49/Pre-	All	65	75
50/Post-	All	56	56
49/Pre-	1–3	86	87
49/Pre-	4	40	51
50/Post-	1–3	68	61
50/Post-	4	40	45

5/78

(*Note*: Courtesy of Dr. Bernard Fisher and the National Surgical Adjuvant Breast Project.)

ter is commercially available and is believed to bind to the estrogen receptor in the cytosol, translocate to the nucleus, and bind to chromatin but not release easily. Cytoplasmic receptors also are depleted after tamoxifen therapy. It is clear that the effectiveness of antiestrogenic treatment correlates very well with estrogen-receptor positivity. An overall response rate of about 33% is seen, but the rate in ER+, postmenopausal patients is as high as 60%.[15] This is similar to the percentage of tamoxifen response in patients previously responding to hormonal therapy. Patients failing to respond to hormonal therapy usually do not respond to tamoxifen.

Most studies have been done in postmenopausal patients, but benefit in premenopausal patients has not been excluded. The dose is 10 mgm by mouth twice a day and is usually tolerated well. Nausea and vomiting are seen in some patients (12% in one series), hot flushes in about 21%, hypercalcemia occasionally, and mild platelet count depression rarely.

Synthesis

The management of the patient with breast cancer increasingly depends on careful staging taking into account the major prognostic features outlined above. The patient with localized disease, small primary and no axillary nodes is probably best served at present by modified radical mastectomy or radical mastectomy, although studies in progress at a large number of centers are beginning to suggest that less extensive surgery with radiation therapy to the chest wall and nodes may be useful in *selected cases*. Knowledge of the presence or absence of axillary node metastasis and the number of nodes involved is of such central importance to prognosis that procedures which do not provide this information cannot be considered useful at this time.

Premenopausal patients with one or more positive nodes but without evidence of metastatic disease elsewhere should be considered candidates for adjuvant therapy. However, the question of whether adjuvant cytotoxic chemotherapy, immunotherapy, or hormonal therapy should be given and for how long remains in the investigative stage. Adjuvant chemotherapy with CMF cannot be considered of proven value for the general population of patients, and every effort should be made to include these patients in clinical trials to establish the value of adjuvant therapy.

The choice of therapy for the patient with extensive disease also has become more complex. ER+ patients of advanced age with cutaneous, pleural, nodal, early bone, or nodular pulmonary disease may respond well to estrogen administration, and on re-exacerbation, androgen or prednisone. Approximately 25% of these patients will show regression of the tumor when estrogen is stopped—the "rebound" phenomenon, which has also been described after androgen and tamoxifen therapy.

The premenopausal, ER+ patient currently is treated with oophorectomy initially and,

TABLE 11
Metastatic Disease

Premenopausal			Postmenopausal	
ER+	ER−		ER−	ER+
Oophorectomy		**Chemotherapy**	**Estrogen**	
Medical adrenalectomy			**Estrogen rebound**	
Surgical adrenalectomy			**Androgen**	
Antiestrogen			**Androgen rebound**	
Chemotherapy			**Antiestrogen**	
			Progesterone or Corticosteroid	
			Chemotherapy	

upon relapse, adrenalectomy or hypophysectomy. In a series studied at the Medical College of Virginia,[16] medical adrenalectomy with aminoglutethimide and dexamethasone is almost as effective as surgical adrenalectomy and does not preclude a response to surgical adrenalectomy when tumor again progresses. A schematic flow sheet to indicate serial treatment measures for advanced disease is shown in Table 11.

The presence of extensive long bone metastases or vertebral destruction should be handled with radiotherapy to as small an area as possible. Some cases may require prophylatic internal fixation of the femur or humerus. Prompt laminectomy and decompression of the spinal cord in epidural tumors or vertebral collapse is always worthwhile. Chemotherapy rather than hormonal therapy will almost always be required in such cases because of the need for rapid control of the disease to ensure continued ambulation.

CNS involvement can frequently be handled with moderate doses of radiation to the whole brain (3000 rads in 10 fractions), but meningeal involvement may also require intrathecal Methotrexate administration.

Liver metastases, extensive visceral involvement, bone marrow, or interstitial pulmonary involvement present almost insurmountable management problems. However, some patients with liver metastases and marked liver dysfunction respond to cytotoxic drugs and these should be instituted. When the situation is desperate, doxorubicin containing regimens with their higher initial response rate are the current choice. Extensive involvement of more than one organ requires cytotoxic drugs for systemic effect and radiation of painful or obstructing masses of tumor.

Corticosteroids provide some short-term palliation of the patient with interstitial pulmonary involvement. When bone marrow involvement with persistent low blood counts precludes full doses of multiple drugs administered on the usual time schedules, reduction of doses and/or the number of drugs may still provide some means of control.

Some general tenets of management of the patient with breast cancer are summarized in Table 12. In all cases the most critical aspect of management is the close support of the patient by an understanding and sympathetic physician.

TABLE 12
Tenets of Breast Cancer Management

1. Make long-term plans for the management of the patient at the onset.
2. Preserve or restore mobility and CNS function.
3. Treatment of painful lesions is virtually always of benefit.
4. Start treatment for local recurrences or systemic disease early; do not delay.
5. Neither despair nor hold out unrealistic promise of cure. Hope is warranted by the facts.

REFERENCES

1. CUTLER SJ, MYERS MH, GREEN SB: Trends in survival rates of patients with cancer. *N Engl J Med* 293: 122–124, 1975.

2. Cancer Facts and Figures. American Cancer Society, 1981.

3. FISHER B, ET AL: Ten year follow-up of breast cancer patients in a cooperative clinical trial evaluating surgical adjuvant chemotherapy. *Surg Gynecol Obstet* 140: 528, 1975.

4. CARBONE PP, DAVIS TE: Medical treatment for advanced breast cancer. *Semin Oncol* 5: 417–427, 1978.

5. HENDERSON IC, CANELLOS GP: Cancer of the breast: The past decade. *N Engl J Med* 302: 17–30, 78–90, 1980.

6. JENSEN EV, DESOMBRE ER: Estrogen-receptor interaction. *Science* 182: 126–134, 1973.

7. MCGUIRE WL: Hormone receptors: Their role in predicting prognosis and response to endocrine therapy. *Semin Oncol* 5: 428–433, 1978.

8. LEGHA SS, DAVIS HL, MUGGIA FM: Hormone therapy of breast cancer: New approaches and concepts. *Ann Intern Med* 88: 69–77, 1978.

9. LEGHA SS, ET AL: Complete remissions in metastatic breast cancer treated with combination-drug therapy. *Ann Intern Med* 91: 847–852, 1979.

10. HOGE AF, ET AL: Adrenalectomy and oophorectomy plus limited-term chemotherapy in the treatment of breast cancer. *Cancer Treat Rep* 60: 857–865, 1976.

11. FISHER B, ET AL: L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. *Cancer* (Suppl.) 39: 2883–2903, 1977.

12. BONADONNA G, ET AL: Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 294: 405–410, 1976.

13. BONADONNA G, VALAGUSSA P: Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med* 304: 10–15, 1981.

14. BONADONNA G, ET AL: Are surgical adjuvant trials altering the course of breast cancer? *Semin Oncol* 5: 450–464, 1978.

15. KIANG DT, KENNEDY BJ: Tamoxifen (Antiestrogen) therapy in advanced breast cancer. *Ann Intern Med* 87: 687–690, 1977.

16. NEWSOME HH, ET AL: Medical and surgical adrenalectomy in patients with advanced breast cancer. *Cancer* 39: 542–546, 1977.

Tapping the Tube

SARA KALTREIDER, MD

The Old Ways

Before percussion and mediate auscultation were discovered, methods of physical examination—in particular chest examination—were limited. Only observation was used with any regularity. From the time of Hippocrates, palpation and direct auscultation had been used sporadically to detect heartbeats but had not proved to be of practical value because clinicopathological correlation had not yet been established. At last, when a new method called percussion was conceived by Auenbrugger in 1761, it was ignored for almost forty years. Not until the French School evolved did percussion become established, largely through Corvisart, Napoleon's private physician. Coincident with the revival of percussion, Laennec, another physician of the French School, invented the stethoscope and mediate auscultation. How remarkable that these two methods of chest examination came into use at the same time and in a period of history when chest disease—especially tuberculosis—was rampant!

Until the mid-seventeenth century systematic instruction in clinical examination was nonexistent; no patient contact was required for medical training or degrees, and it was necessary to pass only an oral test. Two great clinicians, Sydenham and Boerhaave, who practiced in the seventeenth century, helped to change this pattern and emphasized the importance of observation as a method of clinical examination.

Thomas Sydenham (1624–1689), an Englishman, had barely begun his college career when it was interrupted by the Civil War. Four years later when the war between the King and Parliament was over, Sydenham felt too old to start a college education again. "At a loss for a career," he decided to study medicine at Oxford.[1] Because of his war experiences and his brief formal medical education, Sydenham's approach to medicine was practical and relatively unspoiled by the old theorizing which was popular until his time. Sydenham realized the need for practical clinical study as he expressed in his words: ". . . the human mind is far too limited in its ability and knowledge to settle the great problems of what disease is, and why there should be disease. While we debate such questions there are sick men who need help. . . . The place to study disease is at the bedside of the sick man: by observation and experience we can learn the nature of disease."[2] He recorded thorough observations on many diseases including scarlet fever, measles, chorea, smallpox, malaria, and dysentery, but his masterpiece was a meticulous description of gout, a disease from which he himself suffered. Because his style of clinical observation and description resembles that of Hippocrates, Sydenham has earned the title the "English Hippocrates."[3]

Hermann Boerhaave (1668-1738) also stressed clinical observation and popularized bedside medicine. He was born in Holland, the son of a clergyman, began his studies in theology at Leyden, and, becoming interested in the sciences and medicine, he resolved to become a doctor. Respected and loved by his pupils as a physician, he was able to promote new ideas on the nature of disease. "A disease," he said, "is a physical thing and its cause is also a physical thing . . . which induces a change in the solids and fluids of the body."[4] Boerhaave was a pioneer in associating clinical features of disease with post-mortem appearances, although

[I should like to acknowledge the help, encouragement and inspiration given to me by Dr G. J. Cunningham and Dr F. J. Spencer.]

clinicopathological correlation did not reach its full potential until later through the work of Morgagni.

During Boerhaave's time, and still later in the eighteenth century, examination of a patient's unclothed body remained a rarity even in the case of infants. Boerhaave, however, after a history had produced no clues, would resort to physical examination. An account is given of an infant taken to Boerhaave with a fever of unknown origin. After an unrevealing history, he demanded that the infant be undressed, whereby he discovered a needle in its body as the source of infection.[5] Besides observation, Boerhaave instituted other tools in his practice at Leyden; he used the Fahrenheit thermometer, looked at blood and urine under the microscope, and routinely performed autopsies.[6] These methods and ideas were propagated and spread throughout Europe, and his fame extended even to China. His students came from several foreign countries, and his influence on other universities was considerable. Two of his pupils, Van Swieten and de Haen, were responsible for the development of the old Vienna School, and all the founders of the Medical School at Edinburgh trained under Boerhaave. Bedside observation and post-mortem examination became important traditions in these schools, and it was in Vienna that Auenbrugger studied and made his remarkable discovery.[7]

Percussion

Leopold Auenbrugger (1722-1809), born at Gratz in the Austrian province of Styria, was the son of an innkeeper and often helped his father in the inn. He completed his medical studies under Van Swieten at the Vienna School and became an attending physician at the Spanish Military Hospital of the Holy Trinity (1751). This large hospital, the finest in Vienna, provided abundant opportunities for clinical observations, and over a seven-year period, Auenbrugger tested his famous discovery.[8] The idea of percussion came about as Auenbrugger was tapping on wine barrels in his father's inn to locate the fluid level without having to open the barrels. In this manner he could determine when the supply was dwindling, the hollow sound indicating emptiness. He ingeniously applied the new principle of percussion to his patients and found that he could detect consolidation, pleural effusion, and even cardiac dilatation. Not only did he confirm his diagnostic impressions at autopsy, but he also tested his method by injecting fluid into the pleural space in cadavers and then percussing them to find the fluid level.[9]

Auenbrugger published his findings in 1761 in "Inventum Novem," a modest 95-page volume which has become a medical classic. The full translated title of the book is *A New Discovery that Enables the Physician, From the Percussion of the Human Thorax, to Detect the Diseases Hidden Within the Chest.*[10] Auenbrugger's observations are found in Camac's *Epoch-making Contributions to Medicine*[11] and are now summarized. First, a description of the normal chest sound and its characteristics in different areas is presented. In the healthy state this sound is like a "stifled drum covered with a thick woolen cloth." Variation according to body habitus is explained, the sound being more prominent in the lean and almost lost in the obese. The technique for percussion is suggested: the chest is "struck slowly and gently, with the points of the fingers brought close together and at the same time extended." Methods are given for percussing the clothed and unclothed chest, positioning the patient, and instructing him how to breathe. Next, the dull sound called the "preternatural" or "morbid" sound is described. In this part an analogy is drawn between a cask of fluid and a chest with effusion. Other observations relate those diseases producing the dull sound; for example, inflammation of the pleura or lungs, serous, purulent, and bloody effusions, pericardial effusion, cardiac enlargement; and those diseases not causing a dull sound; for example, asthma, consumption, small lesions.

Interestingly, Auenbrugger, with much insight and wisdom, had stated in the preface of his book, "I realize . . . that envy and blame and even hatred and calumny have never failed to come to men who have illuminated art or science by discoveries."[12] Indeed, his masterpiece did not immediately achieve the attention and success it deserved. Van Swieten, to whom Auenbrugger almost dedicated his book, failed to comprehend the value of percussion. De Haen, who lamented the "obscurity and difficulty of diagnosis of thoracic disease," likewise never acknowledged percussion and its possibilities.[13] Others either ignored or grossly misinterpreted the "Inventum Novem" as did

Rudolph Vogel, an authority in medicine in Göttingen, who mistakenly wrote that Auenbrugger's percussion was only a variation of Hippocrates' succussion, and was annoyed that Auenbrugger did not give credit to Hippocrates.[14] The succussion splash known to Hippocrates was a sign pathognomonic of seropneumothorax and heard less often with pyopneumothorax; it really depended on the presence of both air and fluid in the pleural cavity. Hippocrates elicited this sign by shaking the patient's shoulders and either listening from arm's length or with the ear to the chest when he would hear a "splash" or metallic tone.

Despite the lack of enthusiasm for his discovery, Auenbrugger lived a happy life. He was well accepted among his peers for his congeniality and loved by his students for his generosity and compassion. He enjoyed a golden anniversary with his wife, a peaceful retirement in the suburbs, and died at the age of eighty-seven. His method was only temporarily put to rest and was later revived by the French physician, Corvisart. Still later, after percussion had gained popularity, another French physician named Piorry promoted a modified form of Auenbrugger's method, mediate percussion, which is still used by modern physicians.

The French School and the New Medicine

In the last few years of the eighteenth century, France was experiencing a Revolution in medicine as well as in politics. The philosophical mood which favored observation, experience, and skeptical empiricism instead of the classical beliefs, carried over into the field of medicine and the famous French School in Paris.

All remnants of the old regime were swept aside by the Revolution, and the universities and medical colleges closed. A few years later when France was at war, the shortage of doctors became serious, and the only places available for training were the hospitals. The hospitals became "the workshops of new medicine," and according to the historian Ackerknecht, ". . . it was only in the hospital that the three pillars of the new medicine—physical examination, autopsy, and statistics could be developed."[15]

The hospital clinical training as formulated during this period sounds surprisingly similar to today's attending round. "The professor would pause at the bedside of each patient long enough to question him and examine him properly; he would draw the students' attention to the diagnostic signs and the important symptoms of the disease . . . ."[16] The students would "read little, see much, and do much," learning as they practiced at the bedside.[17] Thus the French School gave birth to medicine as it is practiced today, produced many great physicians, and became the leading school in Europe.

The Revival of Percussion

Jean Nicolas Corvisart (1755–1821) was an eminent figure in the French School, and as a proponent of percussion and teacher of Laennec, he became "the connecting link between the men who did the most for the practical science of medicine"—Auenbrugger and Laennec.[18] Corvisart began his career in surgery and anatomy but then turned to internal medicine. In 1782 he was rejected for a position at the Necker Hospital despite excellent qualifications because he refused to wear a powdered wig! However, he successfully held positions in subsequent years at the Charité, École de Santé, and Collège de France.

It was in 1799 that Corvisart came upon Auenbrugger's work through a book by Eyerel, a student of the Vienna School who praised the method of percussion. Giving full credit to Auenbrugger, Corvisart found and translated the original "Inventum Novum" from Latin into French, added to it his own commentaries, and published the entire work in 1808. Two years previously, Corvisart had published a book on heart disease, *Maladies du Coeur,* in which he brilliantly discussed pericarditis, cardiac dilatation and hypertrophy, cardiomyopathy, and valvular and aortic disease. However, by far his greatest gift to modern medicine was the revival and propagation of percussion, so that by 1825 it was in use practically everywhere.[19]

In 1804, Corvisart was selected to be Napoleon's physician, in part because of the Emperor's appreciation of percussion. Corvisart was called into consultation for a persistent cold bothering Napoleon, who was impressed when this great physician used percussion in his examination.[20] In 1815, following the downfall of Napoleon, Corvisart retired from medicine altogether and in 1821 died of a stroke. One of his most outstanding qualities was his ability to in-

spire and encourage his pupils and their ideas. He closely assisted his students, particularly in bedside observation. In this way, Laennec came to know and esteem Corvisart and to become his favorite pupil.

Mediate Auscultation

Rene Theophile Hyacinthe Laennec (1781–1826) was born at Quimper in Bretagne, a province in northern France. His mother, having exposed Laennec to tuberculosis, died of the disease when he was six years of age. Consumption shortened Laennec's life as well but did not hamper his productivity. His father, who was an eloquent lawyer but irresponsible and always in debt, sent his sons to live with their rector grand-uncle at Elliant. At age 11 Laennec went to Nantes to live with his uncle Guillaum Laennec, a physician and faculty member at the University of Nantes who was instrumental in Laennec's decision to study medicine.

Laennec's early education was interrupted by the French Revolution, but at age 19, after much deliberation, he went to the renowned Paris School to study medicine. In the year that followed, he won two prizes given in medicine and surgery at the University of Paris. At age 23 he successfully completed a medical thesis on Hippocrates. Following his formal medical training, he spent four years as physician at Beaujon Hospital in Paris and then obtained a position at the Necker Hospital where he made his famous discovery of mediate auscultation.

The examination of the chest just before Laennec's discovery consisted of inspection, palpation, the newly added method of percussion, and immediate or direct auscultation. Auscultation in this form was known to Hippocrates but was neither popular nor frequently used. It had a number of disadvantages. Some patients, if not most, were unwashed or vermin-infested, making direct contact undesirable. Other patients had a voluminous amount of fat which rendered the method somewhat less useful; furthermore, direct auscultation proved to be an embarrassment to the female patient.

As immediate auscultation "shocked his decency and modesty," Laennec himself used it only in cases of suspected heart disease when the heart beats could not be felt by palpation.[21] In his own words, "(It was) as uncomfortable for the doctor as it was for the patient, disgust in itself making it impracticable in hospitals. It was hardly suitable where most women were concerned and, with some the very size of their breasts was a physical obstacle to the employment of this method . . . ."[22]

The Tube

In 1816, Laennec was consulted at the Necker Hospital by a young female patient thought to have heart disease. On his way to visit this patient, he saw several children playing on some lumber in the gardens of the Louvre, and he was reminded of an acoustic principle. As one child tapped on the beam at one end, the signal reached the other child with his ear on the opposite end. Excitedly, Laennec hurried to the bedside of his patient with a cylinder of tightly rolled paper tied with string and found that by placing this instrument between his ear and the patient, he could hear heart sounds more clearly than ever before. It immediately occurred to him how useful this method might be in studying all movements produced in the thorax—breath sounds, voice, wheezing, pleural and pericardial effusions.[23]

Laennec called the new method "mediate auscultation," "auscultation" for the method in its direct form begun by Hippocrates, and "mediate" for the interposed instrument. The term "auscultate" originated from the Latin "ausis," to hear, and "culto," to cultivate, and meant to give attention through hearing.[24] Laennec named his tool the "stethoscope" combining "stethos" meaning chest and "scope" from the Greek word meaning to examine. Other names initially applied to the invention included "a pectoriloquy," "medical trumpet," "the cylinder," or "the tube."[25]

Laennec and everyone else at the Necker Hospital began experimenting enthusiastically with the tube. He varied the length, width, and central hollow, and decided upon a one-foot cylinder with a quarter inch central space which he accidentally found to be necessary for listening to the voice. A solid cylinder, he discovered, would suffice for heart sounds, breath sounds, and rhonchi; however, breath sounds and rhonchi were augmented with the central hollow plus a cupped shape carved at the end. Many materials were tried—"ebony, cedar, malacca cane, lime wood, glass, various metals, . . . gold-beater's skin . . . ."[26] He even used his

cousin's oboe but finally decided a light beechwood was his preference.[27]

Early in 1818 Laennec, having collected his preliminary observations, demonstrated his new method and instrument to the Société d'École. Though he thought it was premature to publish his findings, he felt he should speak for his work as others were mentioning his invention in various publications. At this time he had recorded an outline for his book and was experienced in separating normal from abnormal chest sounds. In the same year he presented his findings to the Académie Médecine, which appointed a commission for study of the method. Laennec continued to accumulate data and propose new applications for the stethoscope. A key case was that of Madame de Châteaubriand who had recurrent hemoptysis and had been diagnosed by a previous consulting physician as a consumptive in the terminal stage. Laennec, finding no signs of cavitation by stethoscope, confidently diagnosed bronchiectasis; Châteaubriand lived to age 75.[28] This differential diagnosis was encountered now and then and was important to the patient as it made the difference between a life or death prognosis.

In attempting to expand his method's application, Laennec reportedly suggested a means of helping deaf-mutes.[29] He also, on occasion, extended his professional career to include auscultating animals. During his countryside vacations which he took only to convalesce from exacerbations of tuberculosis, he was seen auscultating his dogs, "Kiss" and "Moustache."

In April 1819, he delivered to the publisher the final product of his labors, *De l'auscultation médiate, ou Traité de Diagnostic des maladies des poumon et du coeur fondé principalement sur ce nouveau moyen d'exploration;* also known by the shorter title, *Traité de l'Auscultation Médiate.*[30] To provide the editor with an ample supply of stethoscopes to sell with his book, Laennec spent countless hours at his lathe meticulously making the wooden instruments. The book was ready for sale in August 1819 for 13 francs; and the stethoscopes sold for three francs each.[31] A further edition of his book followed in 1826.

Laennec's stethoscope flourished in many countries: England, where consumption was raging, Germany, Italy, Spain, Holland, Sweden, Russia, Poland and even across the Atlantic in America. About 35 years after its discovery, a binaural model was designed by George Philip Camman of New York. Other varieties refining the original were developed from time to time including the modern diaphragm type.

Laennec's New Signs

Laennec described most of the stethoscopic signs used in modern medicine; not only did he describe them, but as an experienced pathologist he was able to correlate them with autopsy findings, distinguishing numerous conditions including tuberculosis or pulmonary phthisis as it was called then, bronchitis, bronchiectasis, emphysema, asthma, pneumonia, and pleurisy. Here are some of the signs Laennec left to medicine:

Aegophony. Greek aix or aegis = goat + phone = sound, sound similar to the bleating of a goat; heard at the upper border of an effusion.

Amphoric resonance. Latin amphora = a jar, also has Greek derivation, sound resembling that heard when blowing into an open bottle; indicates cavity.

Bronchial respiration. Greek bronchos = windpipe, Latin similar, sound heard over larynx, trachea, large bronchi; increased in pneumonia and dilatation of bronchi.

Cavernous respiration. Latin caverna = a cavern, similar to amphoric breathing, hollow sound; indicates cavity.

Crepitant râles. Latin crepitus = little noises, crackling; pulmonary edema.

Metallic tinkling. Sound as made by sand falling into metal cup; indicates cavity.

Pectoriloquy. Latin pectus = breast + loqui = to speak, voice sounding very close to ear through stethoscope; sign of cavity.

Pleural friction. sound resembling rough surfaces rubbing together; heard in tuberculous pleuritis.

Puerile breathing. Latin puer = boy, respiration heard in child, sonorous with marked inspiration.

Râles. French râler = to rattle, crackling sounds; Laennec described them as moist or crepitant, mucous or gurgling, dry or sonorous (snoring), dry sibilant (whistling); heard in multiple situations depending on character.

Rhonchus. Greek word—snoring, Latin rhonchus = snoring, sound heard in many conditions—pneumonia, tuberculosis, bronchitis . . . .

Vesicular respiration. Latin vesicula = little bladder, breath sounds heard over normal lung fields except over trachea and mainstem bronchi.[32]

The Test of Time

Most of the signs Laennec discovered with his stethoscope have remained important to the modern physician. Some are more frequently used than others; for instance, vesicular and bronchial breath sounds, râles, rhonchi, pleural friction rub, and aegophony. Those signs associated with cavitary disease, however, are less often encountered because of the decline in advanced pulmonary tuberculosis, specifically amphoric or cavernous breathing and pectoriloquy. Two terms have wider clinical application than realized by Laennec: aegophony, heard above pleural effusions, is sometimes found in consolidation; pectoriloquy can be used to detect early pneumonia, atelectasis, and infarction.

Yet another method of chest diagnosis has come to be used since Laennec—the X-ray. With the X-ray the physician has been able to look into the chest and actually see pathologic changes. It enables him to confirm with his eyes what he has heard with his ears and also to detect lesions not producing stethoscopic findings. Even so, the stethoscope remains the most convenient and the quickest method of forming diagnostic impressions, determining the need for further diagnostic work-up, and clinically following disease processes in the chest.

Laennec's auscultation has survived the test of time, and along with Auenbrugger's percussion has become a permanent part of systematic chest examination. The chest and its diseases which for so long were mysteries to the clinician began to be solved with these methods. After Laennec, vast numbers of books on chest disease appeared. Though Laennec did more to elucidate pulmonary than cardiac disease, his invention cleared the way for Corrigan and Stokes of the Irish School to make further advances in the realm of cardiac and pulmonary diseases. Thus, the coincident establishment of percussion and auscultation by the French School has certainly been among the greatest milestones in physical diagnosis, adding two new methods to chest examination and offering new frontiers for the clinicians who followed.

As a final note, new uses may be found for auscultation. A recent author described a new variation combined with carotid phonoangiography. It consists of auscultating bruits with a special microphone connected to an oscilloscope.[33] These bruits are recorded graphically and evaluated in terms of percentage stenosis. This is one non-invasive means of determining which patients with transient ischemic attacks would benefit from caroted arteriography. Thus, auscultation, used in its traditional form with the binaural stethoscope, has developed new applications which may expand further in the future.

REFERENCES

1. HAGGARD HW: *The Doctor in History*. Freeport, New York, Books for Libraries Press, 1962, p 273.
2. HAGGARD, pp 275–276.
3. *Medical Classics*. Baltimore, The Williams and Wilkins Co, 1936–40, p 302.
4. KING LS: *The Philosophy of Medicine*. Cambridge, Harvard University Press, 1978, p 224.
5. KING, p 230.
6. DEBAZ P: *The Story of Medicine*. New York, Philosophical Library, 1975, p 38.
7. GARRISON: *History of Medicine*. 1917, p 310.
8. CAMAC CNB: *Epoch-making Contributions to Medicine, Surgery and the Allied Sciences*. Philadelphia, W. B. Saunders Co, 1909, p 117.
9. WALSH JJ: *Makers of Modern Medicine*. Freeport, New York, Books for Libraries Press, 1907, pp 63–64.
10. WALSH, p 61.
11. CAMAC, *Epoch-making Contributions to Medicine, Surgery and the Allied Sciences*, p 125.
12. WALSH, *Makers of Modern Medicine*, p 67.
13. WALSH, p 70.
14. BAAS JH: *Outlines of the History of Medicine and the*

Medical Profession. New York, J. H. Vail and Co, 1889, pp 71–72.

15. ACKERKNECHT EH: *Medicine at the Paris Hospital 1794–1848*. Baltimore, The Johns Hopkins Press, 1967, p 15.

16. FOUCAULT M: *The Birth of the Clinic*. New York, Pantheon Books, 1973, p 71.

17. FOUCAULT, p 71.

18. WALSH, *Makers of Modern Medicine*, p 76.

19. ACKERKNECHT, *Medicine at the Paris Hospital 1794–1848*, p 84.

20. WALSH, *Makers of Modern Medicine*, p 76.

21. KERVRAN R: *Laennec: His Life and Times*. New York, Pergamon Press, 1960, p 133.

22. KERVRAN, p 134.

23. KERVRAN, p 134.

24. SKINNER HA: *The Origin of Medical Terms*. Baltimore, The Williams and Wilkins Co, 1961, p 53.

25. KERVRAN, *Laennec: His Life and Times*, pp 135–153.

26. KERVRAN, p 139.

27. KERVRAN, p 139.

28. KERVRAN, p 141.

29. KERVRAN, p 144.

30. KERVRAN, p 144.

31. KERVRAN, p 148.

32. CAMAC, *Epoch-making Contributions to Medicine, Surgery and the Allied Sciences*, pp 167–200; Kervran, *Laennec: His Life and Times*, p 144; Skinner, *The Origin of Medical Terms*, pp 23–356.

33. PERSSON AV: Stopping the Stroke before it Strikes. *Resident and Staff Physician*, March 1979, p 44.

Colonial Cultivation and Concoctions

SARA JONES GOMBERG, MD

Have you ever wondered how to increase the value of your property? One way would be to include a well-cultivated herb garden, that is if you were a seventeenth-century colonist. Not only were the herbs much sought after for their culinary uses but also for their medicinal properties. Today's medical library may not include a collection of botany books, yet botanical knowledge was a large part of early medical training and the mainstay of the "cavalier concoctions" used by colonists for medical treatment.

In gathering together its first 225 settlers to go to America, the directors of the Virginia Company of England instilled a sense of responsibility in these adventurers to discover plants for medicinals. A few colonists were lured by the prospects of a profitable drug trade. After all, the Spaniards were doing well and had a monopoly on the drugs and spices from South America, in addition to the gold. They were even attempting to block the transplanting of the New World plants. Besides profits, the Virginia Company did have some concern for the health and welfare of these first settlers, and of the first 225, seven were medical professionals.

The medical profession in England had, at that time, emerged as three distinct groups: the apothecaries, physicians, and barber surgeons. The development of these three groups is a topic unto itself. Briefly, the word "apothecary" goes back to Norman times, meaning anyone who kept a shop of such non-perishable commodities as spices, drugs, comfits, and preserves. At the time of the "Jamestowne expedition," the apothecaries were incorporated with the Grocers Guild, hence the apothecary's interest in spices and such. In 1617, James I granted the apothecaries a separate charter. At various times throughout the seventeenth century, the apothecary emerged as not only the dispenser of medicine but also as the general practitioner of medicine.

The physicians were the elite of the original groups. They did not want to concern themselves with "general practice," yet they did not want the apothecaries to sell medicine without a prescription from a physician. The physician, in a classical sense, was the best educated and had behind him the tradition of the Royal College, which had been founded in 1518.

The barber surgeons had been organized since 1540 and were the least educated of the three. They assumed responsibility for any "mechanical" treatment needed by their clients. From the three groups, at times rivaling one another, the Virginia Company attracted seven members. These were apothecaries Thomas Field and John Harford, the physician Walter Russel, and four barber surgeons: Will Wilkinson, Thomas Wotton, Post Ginnat, and Tho Cowper. Only one of the barber surgeons was included among the 144 passengers who first came to Virginia in 1607, and the remainder of the professionals were members of the second sailing in January 1608.

Times were rigorous for these early colonists, and their famines, unfamiliar fevers, and flixes took their toll. By January 1608, when the first supply ship arrived, only 38 of the original settlers were still alive. The surgeon who accompanied the first expedition is not mentioned after 1607 in any extant records. The two apothecaries and one physician mentioned before were not noted in the records, and it is presumed that they, like the majority of the new inhabitants, did not survive. Because these settlers had to treat their ills as best they could with little medical guidance and few materials, there was the impetus for them to discover native plant remedies.

The colonists made requests to the Virginia Company to send them medical supplies and personnel, but communications being what they were, they did not receive their next physician, Dr Lawrence Bohun, until 1610. Trained in Leyden, Bohun was a well-educated man who stayed for only one year in Virginia before returning to England. It is uncertain how much

he added to the well-being of the colony as he spent most of his time investigating the medicinal properties of the local plants. He experimented with a white clay that he claimed had absorbent and "alexipharmic" properties. His vegetable remedies included the abundant sassafras and *Galbanum mechoacon* or rubarbum alum. Rubarbum alum was thought to be good for the "purginge of fleame and superfluous matter."

Bohun returned to England with Lord Delaware, leaving the colonists without any medical authority for the period from 1611 to 1621. Again, they complained of their plight to the Virginia Company. Dr Bohun was appointed Physician-General in 1620 but was killed *en route* when Spaniards attacked the ship on which he was traveling. In 1621, John Potts was selected to replace him. He was accompanied by an apothecary, Joseph Fitch, and on his arrival took on one of the colonists, Mr Townsend, as an apprentice. But once more disaster intervened as Joseph Fitch was killed in the Indian Massacre of 1622. There is no record of Mr Townsend's practicing as an apothecary, and indeed, of no practicing apothecary until the eighteenth century. This is probably related to the collapse of the Virginia Company in 1624, after which there would have been a lack of organized travel facilities for prospective emigrants and no promises of profit which might have attracted medical professionals.

The colonists were, therefore, left to take medical care into their own hands both for themselves and their families. Anyone who showed skill in the treatment of disease or ability in the use of local plant remedies quickly became recognized. The local Virginia legislature responded by passing a law in 1632 that required the parish minister to assist the sick. Occasionally a supply ship's surgeon, while in port, would care for the sick colonists or might even settle in the colony himself. If he did, he was generally considered a ship's surgeon "that knows nothing above the common remedies—not acquainted with plants or the other parts of the Natural History to be any service to the worlde."

As the plantation system developed, it became necessary for the owners to become well versed in the local remedies to preserve the health of their family and servants. A number of publications appeared for the purpose of assisting these owners including *Every Man His Own Doctor or the Poor Planter's Physician* printed in Williamsburg in 1734. The Virginia colonists were developing their own style of society in which the medical practitioner was both a tradesman and a craftsman. This combination prevented the establishment of the guild system under which their English counterparts would be either an apothecary, physician, or barber surgeon, but not all three. The physicians regarded themselves as professionals, the apothecaries were craftsmen, and the barber surgeons were considered tradesmen. On the other hand, the Virginia practitioner did what was needed, diagnosed his cases, dispensed his own medicines, and engaged in what surgery he could. He was a multi-specialist.

As the colonists started to prosper, less time had to be spent on mere survival, and with increasing prosperity a plantation owner might be able to afford to send his son abroad for five to six years of medical education. Whether learning medicine by the apprentice system in Virginia or studying at one of the major European universities, the student was still exposed to botany which remained a significant part of the curriculum. Even those who trained to be physicians in the European sense often had such titles as surgeon-apothecary or physician-apothecary when they returned to Virginia to practice. Usually these new physicians retained their keen interest in botany, not only out of a need to find remedies to cure New World ills, but also for the purpose of classifying the abundant flora. The improving conditions in America gave these developing "aficionados" the opportunity to increase their knowledge of plants. At that time there was growing world interest in the classification of fauna and flora, and it was frequently the physician, astute in botany, who made significant contributions.

Dr John Clayton of Gloucester County, a self-educated physician, wrote what is considered to be the best treatise on American plants, namely *Flora Virginica*. It was first published in 1739 in Leyden under the name of a Dutch botanist. Hence, Dr Smith-Barton is credited with the first "notable" American treatise on the subject —"Elements of Botany," published in 1803. He was a professor of medicine at the University of Pennsylvania and was noted for his

objections to the popular theory of "similia similibus" or "like by like." This implied that every country possessed the remedy for the diseases which prevailed there. A fine example of this is *Polygala Senega* or rattlesnake root. Not only was this plant found in the terrain inhabited by the rattlesnake, but the observer, with a little imagination, might conclude that the root looked like the tail of a snake.

Both Dr John Mitchell of Urbanna, Virginia, and Dr Alexander Garden of South Carolina contributed vastly to the describing of new genera of plants. Dr Mitchell is credited with 25 genera of plants, and he also described the life cycle and reproductive mechanism of that curious American animal, the opossum. He was well educated, having been trained in Edinburgh, and subsequently having made contributions in other areas of natural history. Dr Garden also studied at the University of Edinburgh. He is described as the "parable of the opportunities, temptations and limitations of American life." He was perhaps the most accomplished American botanist of his time, yet he never produced a significant systematic work. Most of his correspondence was via letters to other notable naturalists, and hence his name appears more often than any other American in the famous work by the Swedish botanist, Carl Linnaeus, entitled *Systema Naturae* (12th edition). Dr Garden is remembered by many for the sweet smell of the gardenia, a flower which bears his name.

Plant identification and description were also tempered by the accepted medical practice of the time. In 1760, Dr William Douglas described the traditional approach as "bleeding, vomiting, blistering, purging, and anodynes, etc., and if the illness continued there was repetendi, and finally murderandi." Another physician, John C. Lettsom, who lived in England at this time, summed up the common theories thus:

When any sick to me apply,
I physicks, bleeds, and sweats 'em.
If after that they choose to die,
What's that to me? I Lettsom.

Bleeding was done by the ubiquitous leech or by a special instrument known as a fleam. The colonists, already concerned with preventive medicine, would bleed themselves often according to a schedule in hopes of preventing an affliction. There seemed no limit to the amount a person could be bled except exsanguination. It has been said that George Washington, who had pneumonia, was probably bled to death as a "cure" for his infection.

Bleeding may have been popular, but equally in demand were emetics. There were many "excellent" agents available to induce vomiting. The most widely used at that time, and a drug still recognized today, was tartar emetic (antimony potassium tartrate). In addition to its properties as an emetic, it was used to treat parasitic infections and today is of use intravenously as a treatment for schistosomiasis, mainly of the japonicum type. Although inexpensive and effective, its application is limited by highly toxic side effects including exfoliative dermatitis, toxic liver necrosis, and toxic myocarditis.

Ipecacuanha, another popular emetic, is well known to today's pediatrician. Its original use was not only as an emetic but also as a treatment for diarrhea. The native Brazilians had recognized its effectiveness in dealing with this symptom probably in cases of amebiasis and sold it in 1658 to the French as a secret remedy for dysentery. The source of the "secret" remedy is the dried rhizomes of *Cephaetis ipecacuanha* or *Acuminata ipecacuanhae*.

These two methods, bleeding and vomiting, were used in hopes of ridding the body of its poisonous affliction, and if they failed, the colonial physician could resort to blistering. For this purpose, mustard seeds were ground and mixed to form a paste which was applied to the skin in the form of a poultice or plaster. If the mustard seed failed to draw the poison to the surface, a paste made from dried Spanish Fly (Lytta cantharida vesicatoria) was applied to the skin. This was considered a powerful vesicant and surely would not fail, and if taken internally, it had the additional properties of a diuretic and aphrodisiac.

Diaphoresis was another means of expelling the unwanted humors from the body, and a tea made from the root bark of Sassafras served the purpose well. The overtaxed colonist, as well as the physician, found use for this for an interesting reason. When English goods were boycotted in an attempt to repeal the Townsend Acts, there was a shortage of fine English tea, and Sassafras was substituted. The

colonists soon realized that Sassafras was better left off the shelf as a medicinal, but their desire for English goods did not stop a revolution. Although diaphoresis was desirable, fevers were not, and for these, the sought-after remedy was cinchona or "Peruvian bark." The colonial physician had the Jesuit missionaries to thank for recognizing its properties in curing malaria or relapsing fever. The active ingredient, not known at the time, was quinine, and today a derivative of it, namely quinidine, is used as an antiarrhythmic and as a means to relieve muscle cramps.

Cathartics, also known as purgatives, were a great mainstay of treatment, and the colonial physician frequently relied on botanical remedies such as jalap, ipecacuanha, and rhubarb. In some instances, cathartic concoctions were significantly popular to carry the name of the originator. One example is P: Rudii, a rolled pill named after Eustachius Rudius, and it contained colocynth (also known as bitter apple and bitter cucumber), Scammony (residue of the plant *Convolvulus Scammonia*), Turpeth root, Socotrine aloes (from an aloin), cinnamon, cloves, spirits of wine, salt of tartar, and Black Helebore root. It was claimed that it was even effective in the treatment of some "social diseases."

Pain relievers and sedatives were just as much in demand then as they are today, and opium headed the list. The abundant "Jamestowne weed," *Datura stramonium* was the local source of a narcotic-like drug. It was a sedative and anti-spasmodic in small doses, but in higher doses it was hallucinogenic, though colonists praised this plant for its "cooling effects." For the more minor pains, the physician might rely on a local anesthetic; for example, the pain of a common sore throat was relieved by a gargle prepared from alum. In colonial days a more drastic use of alum was to pack the uterus in case of post-partum hemorrhage, but in modern times it is a spice used in canning.

No list of medicines would be complete without mentioning three of the more all-purpose substances praised by the early colonists and used by the colonial physician to maintain his patients' general well-being. *Polygala Virginina*, better known as seneca rattlesnake root was considered a reliable treatment. Its application was varied, and its reputation, according to William Byrd II, "increases every day." Byrd noted that, "The tincture of it has done wonders in the gout------. By its purging, its diuretick, and diaphoretick qualities it is of great use in the dropsy----- of great efficacy in Pleuretick Feaver ------ (and) a specifick against worms------ for the bite of a mad dog------ it may be perhaps as sure a remedy, as for the bite of a rattlesnake."

Byrd also commented on the attributes of the popular aromatic licorice-like woodland herb, ginseng: "The earth has never produced any vegetable so friendly to man as Ginseng. I have found it very cordial and reviving after great fatigue, it warms the blood, frisks the spirits, strengthens the stomach and comforts the bowels exceedingly. All this it performs without any of those naughty effects that might make men too troublesome to their poor wives."

Although the colonial physician may not have recognized the lack of medicinal value of rattlesnake root and ginseng, he probably never doubted the increasing popularity of tobacoo. Tobacco was the New World plant that would make men rich. Little did the early colonist guess its future role in medicine. Tobacco was not only profitable as a luxury commodity but also as a remedy, for it "purgeth superfluous fleame and other gross humors, openeth all the pores and passages of the body . . . ." It was also claimed that tobacco could heal gout and ague, cure hangovers, and reduce fatigue and hunger. Of the more than 2,000 agents identified in tobacco, the best known is nicotine, which may decrease fatigue and curb the appetite. Despite the custom of not inhaling, the seventeenth-century smoker spent much more time tending his long slender pipe which may have kept him from falling asleep or eating too much. Tobacco probably did little for the colonist's swollen great toe or the fevers of malaria. Who would have thought that such a profitable weed could lead to some of the terminal diseases of today?

The colonists were certainly imaginative in their approach to medical treatment, drawing both on the standard remedies, as well as native plants. What emerged was a multi-specialist apothecary-physician, vital to the community as were cultivation and identification of the local plants to him. One has only to think of how frequently digitalis is prescribed to realize that even as modern physicians without an herb gar-

den in our backyard, we certainly have one in our doctor's bag.

Transcribed from a talk given in a Senior Elective in the History of Medicine at the Medical College of Virginia, May 1980. Sources used in preparation were:

Blanton, W.B. *Medicine in Virginia in the Seventeenth Century.* Richmond, William Byrd Press, 1930.

Boorstin, D.J. *The Americans: The Colonial Experience.* New York, Vintage Books, 1958.

Ford, T.K. *The Apothecary in Eighteenth-Century Williamsburg.* Williamsburg, Colonial Williamsburg Foundation, 1965

Gill, H.B., Jr. *The Apothecary in Colonial Virginia.* Charlottesville, University Press of Virginia, 1972.

Every Man His Own Doctor, 2 ed. Williamsburg, Printing Office, 1971 (reprint of 1734 edition)

Bill Cabbell, Curator, Colonial Williamsburg Apothecary Shop (personal communication)

Volume Sixteen

SUBJECT INDEX

ANTENATAL
. . . genetic studies, 1

AUSCULTATION
tapping the tube, 106

BIRTH CONTROL
contraception versus sterilization, 27

BREAST
. . . cancer, an update, 98

CANCER
breast . . . , 98
cervical cytology and colposcopy, 43
changing concepts, 86
chemotherapy, 78
evaluation and management of adnexal masses, 49
psychological aspects of . . . , 52

CHEMOTHERAPY
cancer . . . , 78

COLONIAL MEDICINE
drugs and concoctions, 113

DIAGNOSIS
cervical cytology and colposcopy, 43
office endometrial sampling, 46

CONTRACEPTION
. . . versus sterilization, 27

CYTOLOGY
. . . and colposcopy, 43

EIGHTEEN NINETIES
The Gay Nineties, 67

ENDOMETRIOSIS
endometriosis, 32
office endometrial sampling, 46

FEMALE PELVIS
relaxation of supporting structures of . . . , 14

GASTROENTEROLOGY
cancer and . . . 90

GENETICS
antenatal . . . studies, 1

HIGH-RISK GRAVIDA
identification of . . . , 4
management of . . . , 9

HISTORY OF MEDICINE
colonial, 113
stethoscope, 106
Oscar Wilde, 67
percussion, 106
Richmond, 71

HOMOSEXUALITY
The Gay Nineties, 67

INCONTINENCE
relaxation of . . . supporting structures . . . female pelvis, 14

MENSTRUATION
abnormalities of . . . , 24

PERCUSSION
tapping the tube, 106

PHARMACOLOGY
. . . and cancer, 78

PSYCHOLOGY
. . . aspects of cancer, 52

STERILIZATION
contraception versus . . . , 27

STETHOSCOPE
tapping the tube, 106

URINARY INCONTINENCE
. . . in women, 36

WILDE, OSCAR
. . . reconsidered 67

Volume Sixteen

AUTHOR INDEX

Caravati, Charles, M., M.D., 71
Cohen, Stephen A., M.D., 46
Coogan, Emily M., R.N., M.S., OGNP, 4

Diasio, Robert B, M.D., 78
Dunn, Leo J., M.D., 24

Fantl, J. Andrew, M.D., 36

Gomberg, Sara Jones, M.D., 113
Goplerud, Dean R., M.D., 49

Hurt, W. Glenn, M.D., 43, 46

Kaltreider, Sara, M.D., 106
Kumarasamy, Thampu, M.D., FRCS, FRCOG, MRCP, 27

Nelson, Kinloch, M.D., 71
Nichols, David H., M.D., 14

Petres, Robert E., M.D., 4

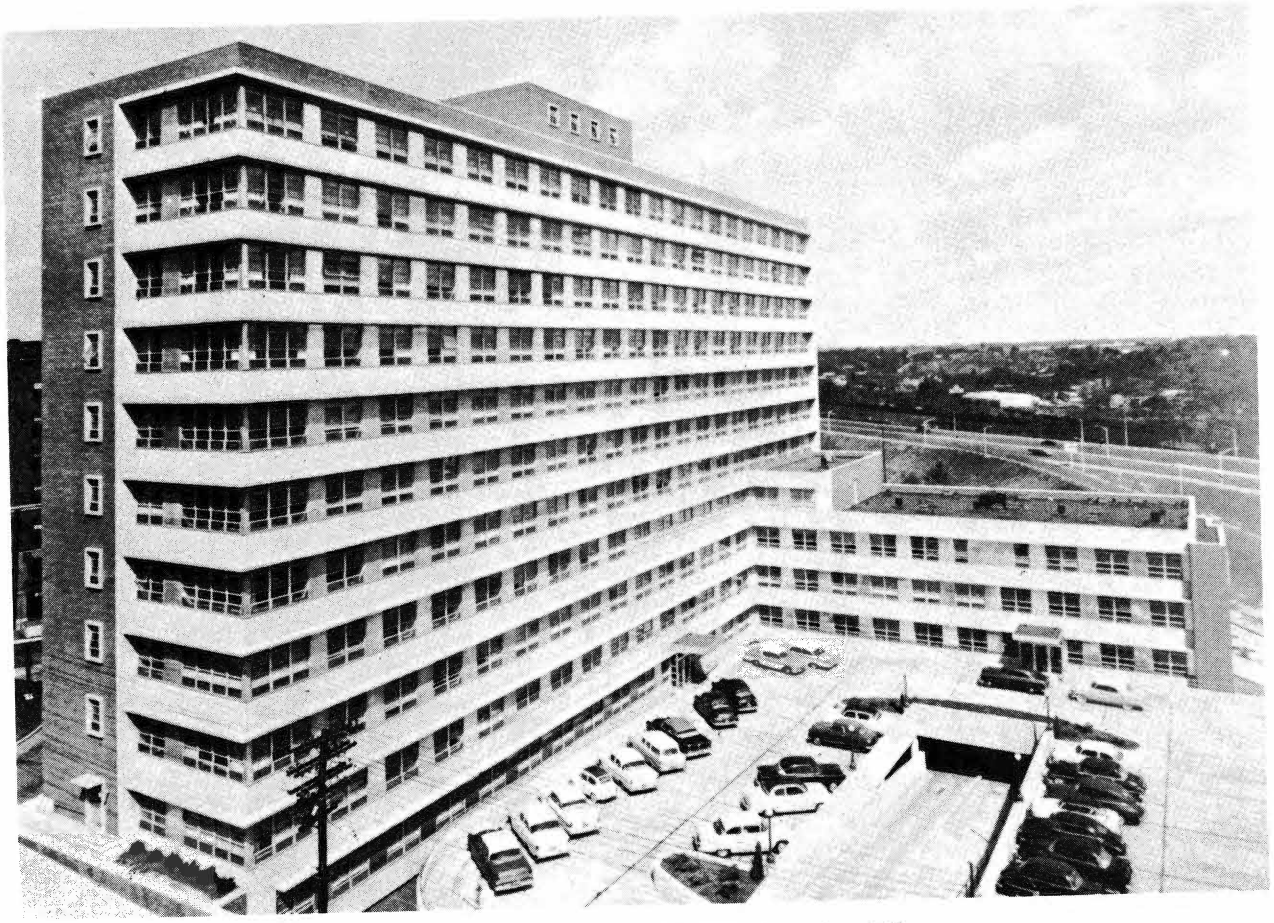
Redwine, Fay, M.S., M.D., 1

Silverman, Joel J., Md., 52
Smith, Wade, M.D., 98
Spencer, Frederick J., M.D., M.P.H., 67

Taub, Robert N., M.D., Ph.D., 86

Wampler, Galen, Jr., M.D., 90
Wertheim, Ray A., M.D., 32

MCV Hospital (MCV West)—1940



Ennion G. Williams Hospital (MCV North)—1956

Sanger Hall—1963

Nelson Clinic—1967


MCV Campus—THE FUTURE

MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
PO BOX 26 • MCV STATION
RICHMOND, VIRGINIA 23298

Nonprofit Org.
U.S. Postage Paid
Permit No. 930
Richmond, Va.

CONTENTS

Volume Sixteen • Numbers Three and Four

The Gay Nineties: Oscar Wilde Reconsidered 67
FREDERICK J. SPENCER, MD

Medicine in Retrospect 71
[*This article is a transcript of an informal talk by Drs Kinloch Nelson and Charles Caravati Presented in 1974*]

Recent Advances in Cancer Chemotherapy 78
ROBERT B. DIASIO, MD

Changing Concepts of Cancer Biology, Diagnosis and Treatment 86
ROBERT N. TAUB, MD, PHD

Recent Advances in Gastrointestinal Cancer 90
GALEN L. WAMPLER, MD

Breast Cancer: An Update 98
WADE K. SMITH, MD

Tapping the Tube 106
SARA KALTREIDER, MD

Colonial Cultivation and Concoctions 113
SARA JONES GOMBERG, MD