

**ADVANCES** *IN*  
***Internal Medicine***<sup>®</sup>

VOLUME 24

# ADVANCES *in* INTERNAL MEDICINE®

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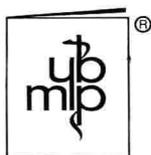
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## ADVANCES IN INTERNAL MEDICINE

VOLUMES 1 through 20 (out of print)

### VOLUME 21

- TRANSIENT CEREBRAL ISCHEMIC ATTACKS, *by Gary W. Duncan, Michael S. Pessin, J. P. Mohr and Raymond D. Adams*
- PULMONARY BIOPSY, *by Donald C. Zavala*
- THE DIAGNOSIS AND MANAGEMENT OF GASTROESOPHAGEAL REFLUX, *by Sidney Cohen*
- INHERITABLE DISORDERS OF BILIRUBIN METABOLISM, *by James B. Israel and Irwin M. Arias*
- MOLECULAR PATHOLOGY OF THE THALASSEMIAS, *by Bernard G. Forget*
- INFECTIONS BY ANAEROBIC BACTERIA OF THE BOWEL, *by Jay S. Goodman*
- ANERGY AND INFECTION, *by Ward E. Bullock*
- THE ONGOING PROBLEMS OF HOSPITAL INFECTIONS, *by William Schaffner*
- HUMAN CANCER VIRUSES, *by George Miller*
- HIRSUTISM AND HYPERANDROGENISM, *by James R. Givens*
- MULTIPLE ENDOCRINE ADENOMATOSIS IN SYNDROMES, *by R. Neil Schimke*
- THE OVERWEIGHT PATIENT, *by G. A. Bray*
- ERYTHROCYTOSIS ASSOCIATED WITH NORMAL BLOOD-GAS VALUES, *by Robert D. Lange*
- THE ANGINAL SYNDROME WITHOUT EVIDENCE OF CORONARY ARTERY DISEASE, *by James H. Gault and Richard D. Gentzler, II*
- ACUTE BACTERIAL DIARRHEAS, *by Richard B. Hornick*
- CHANGING VIEWS OF THE SPECTRUM AND MANAGEMENT OF ATHEROSCLEROTIC CORONARY ARTERY DISEASE, *by Charles E. Kossmann*
- SENILE AND POSTMENOPAUSAL OSTEOPOROSIS, *by Louis V. Avioli*
- RECENT ADVANCES IN ABDOMINAL ANGIOGRAPHY, *by Robert A. Novel-line, Arthur C. Waltman, Christos A. Athanasoulis and Stanley Baum*
- CLINICAL IMPLICATIONS OF RED CELL SHAPE, *by Lawrence S. Lessin, Panpit P. Klug and Wallace N. Jensen*
- THE ENTEROHEPATIC CIRCULATION OF BILE ACIDS IN MAN, *by Alan F. Hofmann*

### VOLUME 22

- ANKYLOSING SPONDYLITIS AND REITER'S SYNDROME: THEIR INTERRELATIONSHIP AND ASSOCIATION WITH HLA B27, *by Rodney Bluestone and Carl M. Pearson*
- CHANGING EPIDEMIOLOGY AND NEWER ASPECTS OF INFECTIVE ENDOCARDITIS, *by Chatrchai Watanakunakorn*
- IMMUNE COMPLEXES IN INFECTIOUS DISEASES, *by William P. Reed and Ralph C. Williams*
- INFECTIONS IN THE COMPROMISED HOST, *by Walter T. Hughes*
- LYMPHOCYTE SURFACE MARKERS IN HUMAN DISEASE, *by Alexander S. Townes and Arnold E. Postlethwaite*

- THYMOSIN AND THE ENDOCRINE THYMUS, by *Richard S. Schulof and Allan L. Goldstein*
- IMMUNOTHERAPY OF HUMAN CANCER, by *Evan M. Hersh, Jordan U. Gutterman and Giora M. Mavligit*
- PREVENTION AND TREATMENT OF THROMBOSIS, by *Stanford Wessler*
- VON WILLEBRAND'S DISEASE—A COMMON BLEEDING DISORDER, by *Eric C-Y. Lian*
- SIDEROBLASTIC ANEMIA, by *James P. Kushner and George E. Cartwright*
- SOMATOSTATIN: DIABETES AND ACROMEGALY, by *John E. Gerich*
- CONCEPTS OF PATHOGENESIS OF GRAVES' DISEASE, by *David H. Solomon and Karen E. Kleeman*
- SPONTANEOUS HYPOGLYCEMIA IN MAN, by *Thomas J. Merimee*
- A RATIONALE FOR THERAPY OF ACUTE MYOCARDIAL INFARCTION: LIMITATION OF INFARCT SIZE, by *Thomas A. Gillespie and Burton E. Sobel*
- DISEASE OF SMALL AIRWAYS, by *James Dosman and Peter T. Macklem*
- PATHOGENESIS OF DIVERTICULAR DISEASE OF THE COLON, by *Alastair M. Connell*
- DIET AND CANCER OF THE GASTROINTESTINAL TRACT, by *Ernst L. Wynder, Bandaru S. Reddy, G. David McCoy, J. H. Weisburger and G. M. Williams*
- ACUTE AND CHRONIC HEPATITIS: MULTISYSTEMIC INVOLVEMENT RELATED TO IMMUNOLOGIC DISEASE, by *Seymour M. Sabesin and Michael J. Levinson*
- PSEUDOMEMBRANOUS ENTEROCOLITIS (ANTIBIOTIC-RELATED COLITIS), by *John G. Bartlett and Sherwood L. Gorbach*

## VOLUME 23

- HISTAMINE H<sub>2</sub>-RECEPTOR ANTAGONISTS, by *Mark Feldman and Charles T. Richardson*
- BREATH TESTS IN GASTROENTEROLOGY, by *Gershon W. Hepner*
- MEDICAL COMPLICATIONS OF INTESTINAL BYPASS SURGERY, by *Telfer B. Reynolds*
- THE ENDOCRINE CONTROL OF GASTROINTESTINAL FUNCTION, by *William Y. Chey and Jorge G. Gutierrez*
- ECTOPIC HORMONES, by *Marc R. Blackman, Saul W. Rosen and Bruce D. Weintraub*
- TREATMENT OF DIABETIC KETOACIDOSIS WITH LOW DOSE INSULIN, by *Abbas E. Kitabchi*
- HYPOPHOSPHATEMIA, by *Faith T. Fitzgerald*
- CALCITONIN IN CLINICAL MEDICINE, by *Leonard J. Deftos*
- THE TRANSPLANTED KIDNEY, by *Jean Hamburger, Jean Crosnier and Béatrice Descamps*
- PHYSIOLOGIC AND BIOCHEMICAL PROFILE OF HYPERTENSION FOR RATIONAL CLINICAL MANAGEMENT, by *Jay M. Sullivan*
- PLATELET FUNCTION INHIBITORS: THEIR CLINICAL USE, by *Valentin Fuster and Paul Didisheim*
- USE OF HEMATIN IN ACUTE ATTACK OF THE "INDUCIBLE" HEPATIC PORPHYRIAS, by *C. J. Watson, C. A. Peirach, I. Bossenmaier and R. Cardinal*

- HYPOVENTILATION: CONSEQUENCES AND MANAGEMENT, by *Clifford Zwillich, Meir Kryger and John Weil*
- NONCARDIAC PULMONARY EDEMA, by *Eric S. Overland and John W. Severinghaus*
- THE IMMUNOLOGY OF THE HEPATITIS VIRUSES, by *Lewellys F. Barker, Robert J. Gerety and Edward Tabor*
- SLOW INFECTIONS OF THE NERVOUS SYSTEM, by *Richard T. Johnson and Volker Ter Meulen*
- THE END OF SMALLPOX, by *Gordon Meiklejohn*
- BACTERIAL VACCINES AND TOXOIDS: REVIEW OF SAFETY AND EFFICACY, by *Gene H. Stollerman*
- NEOPLASIA, AUTOIMMUNITY AND THE IMMUNE RESPONSE, by *Jirayr R. Roubinian and Norman Talal*
- THE TREATMENT OF LUNG CANCER, by *C. Gordon Zubrod and Oleg Selawry*

## Editors' Preface

THE EDITORS present Volume 24 of *ADVANCES IN INTERNAL MEDICINE* with intense awareness of the number of timely topics that we could not fit into this year's reviews, but with considerable gratification about the usefulness of those we have chosen. It is noteworthy that clinical pharmacology and diagnostic methodology dominate the volume and that the grouping of articles by subspecialty interests is inappropriate because of the articles' broad relevance to general medicine and because of their multidisciplinary interfaces.

For this reason, we present a brief editorial comment about each article in the order of its appearance in the volume and leave to the reader the choice of how to catalog these topics which no internist can afford to leave to others to digest for him.

### HOW ASPIRIN WORKS

After centuries of frustration in the quest for the discovery of the modes of the marvelous actions of salicylates, medicine has been treated to a breathtaking revelation. The explosion of knowledge about the physiology of the prostaglandins and the inhibition of their production by aspirin-like compounds have illuminated the pharmacology of a class of drugs that has been used in medicine since Hippocrates advised his rheumatic patients to chew the bark of the willow tree. We had the good fortune to obtain a commitment from Dr. John Vane and his associates of the Wellcome Research Laboratories in England to review this subject to which they have contributed so richly since their discovery of the inhibition of prostaglandin synthesis by aspirin-like drugs in 1971. Between the time of that agreement and the arrival of the manuscript, Drs. Moncada and Vane and their associates identified prostacyclin, the potent *inhibitor* of platelet aggregation and the opposing force to thromboxane- $A_2$ , the pro-aggregator of platelets. The delicacy of this balance of prostaglandins and the effect upon it of various doses of aspirin-like drugs are creating a pharmacologic explosion in the

field of prevention of thromboembolic diseases. Indeed, we suspect that by the time our readers enjoy this very instructive review, many additional insights may have burst into the literature. The article will, however, get us off and running in the race to keep up with one of the fastest moving fields of pharmacology in medicine.

#### HORMONE RECEPTORS

During the past few years there has been an increasing recognition that many, and probably all, polypeptide hormones act by binding to specific receptor sites on the membranes of their target cells. More recently, it has been recognized also that alterations in both the number and affinity of such receptor sites can markedly influence the effectiveness with which various hormones act. In their review of this rapidly moving field, Dr. Bar and his colleagues discuss the physiologic role of insulin receptors in determining insulin sensitivity and in causing the insulin-resistant states that characterize obesity and acromegaly. They examine the role of endogenous and exogenous insulin in regulating the numbers and affinity of such receptors. Finally, these authors describe two newly recognized diseases in which abnormalities of insulin receptors have been shown to be the primary cause of severe hyperglycemia. With the finding that myasthenia gravis and Graves' disease, as well as familial hypercholesterolemia, can be caused by similar receptor defects, it is apparent that both inborn and acquired errors of plasma membrane receptors will prove increasingly to be responsible for presently idiopathic human diseases.

#### ORAL HYPOGLYCEMIC AGENTS

Few areas of medicine have evoked as much controversy in recent years as the problem of how best to treat the diabetic. With the publication of the University Group Diabetes Program's (UGDP) results on the limitations of treatment of diabetic hyperglycemia, the efficacy and possible toxicity of several of the widely used oral hypoglycemic agents have become the subject of considerable debate. This volume of *ADVANCES IN INTERNAL MEDICINE* presents two viewpoints regarding the conclusions of the UGDP study and by implication, the use of oral agents. Drs. Boyden and Bressler review the current use and metabolism of each of the oral agents and provide a very useful discussion of the interactions between the hypoglycemic agents

and various drugs that may potentiate hypoglycemia, at times to the point of toxicity. The authors conclude that the sulfonylureas and phenformin are not sufficiently effective for therapeutic use in a great majority of maturity-onset diabetics. Having questioned the effectiveness of the oral hypoglycemic agents, Drs. Boyden and Bressler examine the data of the UGDP and clearly agree with the conclusion of this study that the oral hypoglycemic agents cause cardiovascular mortality.

By contrast, Dr. Alvan Feinstein's review strongly questions the validity of the conclusions of the UGDP study. The author points out the unequal distribution of cardiovascular risks among the treatment group at the outset of the study, the failure of the UGDP to evaluate many of the clinically significant cardiovascular signs and symptoms of the patients studied and the failure to correct for patients transferring from one treatment form to another. He also notes that a greater number of autopsies, and hence a more vigorous search for cardiovascular deaths, was carried out among the tolbutamide-treated group. Citing these defects in the UGDP study, Dr. Feinstein questions whether the UGDP has demonstrated that tolbutamide is responsible for the preponderance of cardiovascular deaths observed in the patients treated with this agent. Finally, Dr. Feinstein emphasizes that, unfortunately, the critical question of whether tight control of blood glucose will prevent or delay the vascular lesion of diabetes has not been addressed by the UGDP study and still remains to be answered.

#### PROBLEMS OF THE PILL

With contraceptive pills being used by between 20 and 40% of adult women, it is critical that the internist become aware of the types, modes of action and, at times, serious side effects of the various oral contraceptive preparations. Drs. Durand and Bressler, in their very thorough review of this subject, carefully evaluate these aspects of the estrogenic and progestational as well as the combination and sequential approaches to contraception. The evidence relating contraceptive pills to pulmonary embolism and deep venous thrombosis is weighed carefully, as is the current status of the controversy relating estrogenic contraceptive pills to breast and endometrial carcinoma. Finally, every internist will find the list of relative and absolute contraindications to estrogen contraception to be useful in treating patients.

### STEROID RECEPTORS IN BREAST TUMORS

Hormonal manipulations in management of breast cancer have a long and rich history—back to late in the 19th century when castration was first recommended. Subsequent studies by Loeb and later Lacassagne showed that estrogens have adverse effects on spontaneous breast cancer in female mice. The first reports of use of androgens came 40 years ago. Understanding of the molecular bases for the effects, good and bad, of both estrogens and androgens is now emerging. Dr. McGuire, in the forefront of research in this field, has provided a lucid review of the applications in primary breast tumors of assays of steroid receptors as prognostic monitors and guides to adjuvant therapy. Although only a few other cancers in man are now assayable, the implications of such studies are certain to lead to fruitful application in many other inoperable neoplasms.

### IATROGENIC DISORDERS RESULTING FROM CANCER THERAPY

The cure of most cancers has not been attained. They simply are not resectable by time of diagnosis. Therefore the greatest thrust has been toward improvements in radiotherapy and in chemotherapy with more effective use of older agents and development of new ones. Notable improvements in prognosis with cures in some instances have become commonplace. These accomplishments have been tempered by the development of many iatrogenic disorders. Since vigorous new approaches to cancer are now so widely used, these iatrogenic disorders are now seen by all practicing physicians. Dr. Harrington has provided a timely and succinct review of this largely new field of medicine.

### BONE MARROW TRANSPLANTATION

Among organ transplants, the bone marrow has been among the longest studied with impetus given particularly by the introduction of nuclear warfare. Breakthroughs have not been sudden or startling. Bone marrow transplantation has now reached the point of important application to certain clinical disorders, most notably severe aplastic anemia and severe combined immunodeficiency. Dr. Santos, director of one of the world's most active marrow transplant units, has provided a thoughtful and objective review of the current state of the art at a time when it is most needed.

## DRUG ABUSE

The medical complications of drug abuse can affect almost every organ of the body and thus are relevant to all of the subspecialties of medicine. In his systematic review of this subject, Dr. Becker extensively describes the physical findings that should alert the internist to the drug-abusing patient. Both the acute and chronic complications of a wide variety of frequently used drugs are described in some detail. With the increasing but unsuspected use of drugs throughout the socioeconomic spectrum, Dr. Becker's description of the medical complications of such common drugs as propoxyphene hydrochloride (Darvon) and pentazocine (Talwin), and such exotic drugs as angel's dust, should prove invaluable to internists regardless of their subspecialty.

## THE NEW LOOK OF VENEREAL DISEASE

It is symptomatic of the striking change in the current perception of the prevalent sexually transmitted diseases that Dr. Fred Sparling leaves out of his review many of the "classical" venereal diseases such as lymphogranuloma venereum, granuloma inguinale and chancroid and includes chlamydia, ureaplasma, genital herpes and cytomegalovirus and hepatitis viruses in the list of agents of rising concern in VD control. Changing sexual mores and widespread sexual promiscuity make the venereal transmission of these diseases of increasing importance to all clinicians. Gonorrhoea continues to be of foremost concern, however, and since our last review of the subject by King Holmes five years ago (1974, Volume 19), significant changes in the microbiology of gonococci have been perceived including the terrifying threat of the spread through the United States of the oriental penicillinase-producing strain. Dr. Sparling reviews the rapid progress being made in our understanding of the microbiology of gonococci, its host-parasite relationships and its changing epidemiology, particularly the disturbing finding of asymptomatic urethral carriage in the male. The clinical microbiology of nongonococcal urethritis, cervicitis and salpingitis is also ably reviewed and the current problems in the recognition, treatment and management of syphilis are highlighted. The frustrating problem of genital herpetic infection is given particular emphasis because, as Dr. Sparling so aptly phrases it, this agent has "replaced syphilis as the infection most likely to promote sexual fidelity."

## ANTIVIRAL CHEMOTHERAPY

The hungry quest for antiviral chemotherapy has generated many disappointments by overenthusiastic investigators. The rigidly controlled clinical trials so necessary for proof of efficacy but so difficult to achieve in serious illnesses for which there is no effective alternative therapy, have been extremely difficult to complete. Dr. James Luby critically reviews agents that appear to have therapeutic and/or prophylactic value against viral diseases in man. Amantidine is already well established as a chemotherapeutic agent for influenza and one of possible therapeutic value if given very early in the disease. Methisazone is clinically effective both therapeutically and prophylactically in smallpox, but as we told you last year, smallpox has disappeared! Idoxuridine (IDU) and Ara-A have some value in the topical therapy of herpes simplex keratitis. IDU and Ara-C when used systemically for treatment of herpes simplex encephalitis failed to withstand the rigors of a test of efficacy by a double-blind controlled trial. Ara-A, on the other hand, has been proved effective but is mutagenic and teratogenic and must be reserved for destructive illnesses. Other agents such as inosiplex and levamisole are being used with varying success to stimulate the effector limb of the immune response against viruses but recurrent herpes labialis and genitalis still resist all attempts to stop their painful and frustrating course. Finally, interferon and Ara-A have recently shown promise in the treatment of chronic active hepatitis due to type B virus. Although antiviral chemotherapy is far from spectacular, the fact that there are now several agents of proved value that we can review is a giant step forward.

## POLYCYTHEMIA VERA

Polycythemia vera is a chronic, progressive disease, generally easily diagnosed because of its many hematologic, physiologic and biochemical "handles." It has provided an abundance of insights into related disorders. It has led the curious on many new adventures in human biology. Drs. Hoffman and Wasserman are among today's most distinguished such adventurers. They have written an excellent summary on pathogenesis, diagnosis and treatment of polycythemia vera.

## DIGITALIS GLYCOSIDES

By reviewing the pharmacokinetics, pharmacodynamics and clinical applications of digitalis glycosides, Doherty has written a comprehensive update of the clinical pharmacology of a group of drugs that are among the most frequently used in clinical medicine. All physicians who treat failure or arrhythmias of the heart will find this quantitatively oriented review of therapy with digitalis and its derivatives by an internationally recognized expert in the field not only informative but also of considerable practical bedside use.

## ATHLETE'S HEART

The global interest in exercise for health, the phenomenal increase in amateur and professional athletics and the approaching 1980 Olympic games have made it appropriate to include in the present volume a chapter on the perennially disputed issue of the effect of athletics on the heart. Crawford and O'Rourke consider the athlete's heart to be a normal variant, and have described the ways in which it differs from the non-athletic normal heart. These include sinus bradycardia, dilatation of the ventricles, increased cardiac weight, large resting stroke volume and an enhanced cardiac output with exercise. The echocardiograph has helped to resolve the matter of increased internal dimensions of the ventricles but increased thickness of their walls is less certain. Problems in differential diagnosis will come up for the physician who examines athletes for any reason. He may then encounter the task of differentiating organic heart disease with enlargement of the heart from what is found normally in the athlete. The problem is particularly difficult on occasion in the black athlete who, in addition to a large cardiac silhouette on x-ray, may display electrocardiographic abnormalities such as high voltage of the precordial QRS deflections, a juvenile T wave pattern and abnormal elevation of the S-T junction — features often encountered normally in the healthy young black male.

## NONINVASIVE CARDIOLOGY

The trend in the management of cardiac insufficiency has been to attempt to assess ventricular function before it has been

impaired to the extent of calling forth the congestive mechanisms needed to maintain effective arterial blood flow. Of considerable help in this regard has been a variety of noninvasive methods which have reduced the frequency of need for cardiac catheterization and cinecardiography. The far-ranging chapter by Meller, Herman and Teichholz ties together the old noninvasive methods, such as electrocardiography, roentgenography and fluoroscopy, and apex cardiography with the newer ones including the systolic-time intervals, echocardiography, modern exercise electrocardiography, and radionuclide cardiography. The authors evaluate the place of each method in the determination of left ventricular function. They emphasize that these methods often complement rather than substitute for each other, increasing in this manner the accuracy of the determination. This chapter covers the subject in considerable detail and must be read to appreciate the quantitative extent to which the clinician can now evaluate cardiac function.

#### TREATMENT OF CHRONIC RESPIRATORY FAILURE

As a sequel to the chapter on acute respiratory insufficiency by H. L. Davis which appeared in Volume 19, there is in the present volume a chapter on the therapy of chronic respiratory insufficiency by Mariencheck. After defining the term and enumerating the disturbances in respiratory functions encountered with the obstructive and restrictive types and with abnormalities of the respiratory center, the author lists the objectives and the pragmatic details of managing the disabling manifestations and common complications of impaired respiration. Although continuing care of any specific disease causing the insufficiency is most effectively carried out by a therapeutic team, the author points out that not only must the team leader be a physician knowledgeable in all of the modalities of treatment but in many instances, considering the ubiquitous distribution of chronic pulmonary disease, must be capable of carrying out the program more or less single-handedly if any degree of success is to be achieved. The physician who provides care for patients with chronic respiratory insufficiency will find this chapter most helpful in enhancing his capability of providing some symptomatic relief and probably additional longevity to these breathless victims of pulmonary disease.

## HYPORENINEMIC HYPOALDOSTERONISM

The finding of hyperkalemia in the setting of either diabetes or renal disease usually will invoke the diagnosis of renal failure as the cause of elevated serum potassium. It has recently been established, however, that the most common cause of hyperkalemia in the patient with mild renal insufficiency is a depressed secretion of renin by the juxtaglomerular cells of the kidney. In their discussion of hyporeninemic hypoaldosteronism, Drs. Schambelan and Sebastian outline the pathophysiology of this increasingly recognized disorder. They logically explain the basis for the accompanying metabolic acidosis and discuss the impact on serum potassium of the hypoinsulinemia and hyperglycemia that may be present in the diabetic with hyporeninemic hypoaldosteronism. After presenting a comprehensive differential diagnosis of other hyperkalemic states, the authors outline how the diagnosis of hyporeninemic hypoaldosteronism can be established firmly. Perhaps more important, they emphasize that this condition usually can be treated satisfactorily with medications that are readily available to the practicing physician.

## ENTERIC HYPEROXALURIA

Enteric hyperoxaluria now is recognized as the most common cause of increased renal oxalate excretion in man and is associated with the formation of calcium oxalate kidney stones and, occasionally, with progressive renal failure. Hyperoxaluria has been described in a wide variety of gastrointestinal disorders associated with fat malabsorption, including Crohn's disease of the small bowel and jejunoileal bypass. In this chapter, David Earnest provides one of the more definitive expositions of this fascinating subject beginning with a review of oxalate metabolism generally and followed by consideration of the causes of hyperoxaluria, primary and secondary, the pathogenesis of enteric hyperoxaluria, mechanisms of abnormal intestinal oxalate absorption, the site of abnormal oxalate absorption, the consequences of enteric hyperoxaluria and the treatment of this disorder. Therapeutic measures include reduction in dietary oxalate, decrease in fat malabsorption, supplementing the diet with cations (e.g., calcium) to bind oxalate, the use of cholestyramine and various adjuncts. As Earnest concludes, "enteric

hyperoxaluria represents an important new conceptual way to view the syndrome of malabsorption."

#### FLUXES OF FLUIDS AND ELECTROLYTES IN THE GUT

The importance of the gut in the fluid and electrolyte homeostasis of the body, of course, has long been appreciated. The remarkable physiologic, biochemical and physicochemical mechanisms involved in the exchange of electrolytes and fluid from the extracellular fluid across the mucosa into the gut lumen, and vice versa from the lumen through the gut wall into the extracellular fluid, have attracted considerable investigation past and present with new insights appearing steadily. This vast amount of important information now is assembled comprehensively by Phillips and Wingate in one of the more definitive reviews of this subject published in recent years. Malabsorption of electrolytes, loss or abnormalities of the intestinal absorptive surface, abnormal fluid absorption, specific transport defects (e.g. glucose-galactose malabsorption) and intestinal secretion are covered. The clinical disorders discussed include infectious diarrheas, steatorrhea, the Verner-Morrison syndrome, Zollinger-Ellison syndrome, laxatives and other drugs, and intestinal obstruction.

#### CT SCAN OF ABDOMEN

Following the achievement of the EMI scan, the advent of computed tomography (CT) of the abdomen aroused much hopeful anticipation as an important new diagnostic resource. Initial observations, indeed, suggested that this procedure was useful in the recognition of a broad spectrum of abdominal diseases. However, the record is incomplete and conclusive evaluation including comparative diagnostic efficacy with other noninvasive techniques, including ultrasound and radionuclide scanning, will require more time and experience. Sheedy and his colleagues evaluate this procedure on the basis of more than 5,000 CT examinations (65% abdominal) performed at the Mayo Clinic since 1973. This succinct and objective review is carefully organized into descriptions of the normal anatomy of the abdominal and retroperitoneal organs, followed by accounts of the abnormal findings in various diseases and the potential therapeutic applications of abdominal CT, e.g., radiation treatment planning, staging of neoplastic diseases and coordinate application with interventional techniques such as aspiration and biopsy of intra-abdominal masses.