

**ADVANCES *in***  
**INTERNAL MEDICINE®**

**VOLUME 26**

**EDITOR**

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# ADVANCES *in* INTERNAL MEDICINE®

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**VOLUME 26 • 1980**

**YEAR BOOK MEDICAL PUBLISHERS • INC.**  
**CHICAGO • LONDON**

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Library of Congress Catalog Card Number: 42-20729

International Standard Serial Number: 0065-2822

International Standard Book Number: 0-8151-8296

## Editors' Preface

Volume 26 of *ADVANCES IN INTERNAL MEDICINE* marks the twelfth consecutive edition published under the aegis of an editorial board whose composition has remained intact since its appointment in 1968. The retirement this year of Drs. Joseph B. Kirsner and Charles E. Kossmann, Jr. as editors of these reviews posed a formidable challenge to the editorial board and to our publisher. Could we find another gastroenterologist and another cardiologist as highly esteemed by their colleagues in the respective subspecialties, and as highly regarded by all internists as consummate physicians?

Persuading Drs. John S. Fordtran and James J. Leonard to join the editorial board has eased the burden of our loss considerably. They each bring to the *ADVANCES* series the enormous competence and reputation that characterizes their predecessors. We welcome the impetus our new associates will provide to our mission and we salute Drs. Kirsner and Kossmann for the creative critique they infused into a dozen volumes of *ADVANCES* and for the persuasive charm and good humor with which they accomplished their editorial duties.

A brief editorial comment about the articles in Volume 26 in the order of their appearance follows.

### ENDORPHINS AND ENKEPHALINS

The discovery that numerous tissues in man and other animals contain natural opioid polypeptides has brought about a virtual explosion in our knowledge of the various endogenous substances that can serve to control pain. Drs. Kosterlitz and McKnight extensively review these opioids, the enkephalins and endorphins, and suggest their possible clinical applications. They contrast the relatively circumscribed tissue localization of  $\beta$ -endorphin in the hypothalamus and the pituitary with the widespread tissue distribution of the enkephalins in the brain,

spinal column and intestinal tract. The evidence for a physiologic function of the enkephalins is critically discussed, as is the intriguing possibility that the analgesia produced by acupuncture may be the result of enkephalin action. Other potential functions of the opioid peptides are examined, including their possible role in controlling mood, blood pressure and heart rate and, in large doses, motor activity, in a manner similar to that observed with morphine. Although the clinical implications of the opioid peptides remain to be evaluated, it is already clear from Drs. Kosterlitz and McKnight's review that these newly discovered agents play major roles in numerous neuromuscular functions.

#### GALACTORRHEA-AMENORRHEA SYNDROME

Galactorrhea, either as an isolated symptom or combined with secondary amenorrhea, poses a difficult differential diagnosis. The ready availability of the prolactin immunoassay has greatly aided in identifying those patients with galactorrhea and/or amenorrhea in whom prolactin-secreting adenomas of the pituitary are the underlying cause of this symptom complex. In their review of the galactorrhea-amenorrhea syndrome, Drs. Molitch and Reichlin extensively discuss the appropriate diagnostic approach to identifying the cause of galactorrhea and amenorrhea. They review the various drugs and nonpituitary diseases that may lead to this syndrome, and they critically assess the latest radiologic procedures—especially computerized axial tomography (CAT)—used to diagnose pituitary prolactinomas. Finally, the transsphenoidal approach to removing these adenomas, coupled with medical therapy with bromocriptine, has made it possible to treat such patients with increasing success. These new approaches to treating prolactinomas make it increasingly important that the clinician be able to diagnose and assess these tumors accurately. Drs. Molitch and Reichlin's excellent review will greatly help the internist to do so.

#### DIET AND DIABETES

Diet plays a major role in the treatment of the diabetic patient. However, there is understandable confusion today as to what is actually meant by a proper diabetic diet. Until about

1955, diabetic patients were placed on low-carbohydrate, high-fat diets. By 1970 it was recognized that diabetics were better treated if their carbohydrate intake was normal, and over the past ten years increasingly high-carbohydrate, relatively low-fat diets have been shown to result in improved control of diabetes. Dr. James Anderson thoroughly reviews the history of the many diets to which diabetics have been subjected over the years. He examines the mounting evidence that diabetic control is far better when carbohydrate is unrestricted and emphasizes the importance of dietary fiber in the treatment of diabetes. His excellent review of this complex subject, coupled with his specific recommendations for the dietary treatment of the diabetic, should prove invaluable to clinicians treating patients with either adult or juvenile diabetes.

#### ZINC DEFICIENCY

Zinc has long been known to be an essential element in animal nutrition, but it was only in 1974 that acrodermatitis enteropathica in human beings was conclusively demonstrated to be the result of zinc deficiency. Dr. Tasman-Jones' review of the role of zinc in human nutrition presents ample evidence that the symptoms of zinc deficiency are in fact far more common than has been suspected. Clinically significant zinc deficiency most frequently accompanies parenteral hyperalimentation, especially in patients with Crohn's disease. The resulting depletion of zinc will cause or aggravate diarrhea and decrease the rate of wound healing. In addition, zinc deficiency depresses the sense of taste and may impair the immunologic system by producing atrophy of the thymus. There is also evidence that the impotence accompanying renal dialysis may be reversed by administration of zinc. The increasing recognition of the clinical importance of this metal, present in numerous enzyme systems and a component of insulin, should lead to more frequent diagnosis of zinc deficiency and, where indicated, to prompt zinc replacement.

#### MULTIMODAL MANAGEMENT OF CANCER

An increasing number of disseminated cancers are now curable, especially with multimodal therapy. These include chorio-

carcinoma, Hodgkin's disease, diffuse histiocytic lymphoma, Burkitt's lymphoma and acute leukemias, especially childhood lymphoblastic leukemia. The history of how these malignancies, nearly always fatal in the past, can now be successfully eradicated is told by Dr. DeVita and his associates, who are well qualified to do so because they were the first to apply the principles of multimodal therapy to human studies. The extrapolation of data from bacteria to mice to man required over 45 years, with Skipper and his colleagues providing the critical experimental evidence that drugs could cure transplantable tumors in rodents, if dosage and schedules are properly manipulated. These principles have been successfully applied to improved management of some other traditionally nonresponsive cancers (such as mammary and testicular carcinoma and osteosarcoma), combined with surgical extirpation.

#### THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura is a generally fatal disorder whose cardinal features consist of fragmentation hemolysis, thrombocytopenic purpura, migratory neurologic findings, fever and renal failure. Microthrombi are found throughout the body and produce these features. The diagnosis is now made several times each year in large medical centers. The disease is now curable in the majority of patients. Dr. Byrnes, the first to describe the beneficial effects of normal plasma, reviews the history of this startling disorder that seems to be due to an acquired loss of a circulating inhibitor of platelet aggregation. Placed in perspective are the value in management of splenectomy, use of glucocorticoids, antiplatelet agents, plasmapheresis, plasma transfusions, immunosuppressants and platelet transfusions. The inhibitor of platelet aggregation very likely modulates the integrity of small blood vessels in health as well as in other disorders of the microcirculation.

#### TREATMENT OF IRON OVERLOAD

Marked iron overload can lead to complications such as cirrhosis, cardiac dysfunction, endocrinopathies, growth retardation and joint dysfunction. These complications can arise whether the iron excess is due to increased intestinal absorption or to

multiple transfusions. Dr. Brown is a distinguished contributor to new knowledge of iron metabolism. His scholarly review of tests of iron overload, the genetics of primary hemochromatosis and the treatment of iron overload is very comprehensive. Particularly impressive are such ingenious approaches in patients with chronic hemolytic anemia as the use of supratransfusions as well as neocytes and removal of gerocytes and the latest refinements in the use of desferoxamine.

### NON-A, NON-B HEPATITIS

Discovery of the Australia antigen and its identification as hepatitis B surface antigen (HB<sub>s</sub>Ag), by providing a serologic diagnostic tool, revolutionized thinking about B hepatitis virus infections (HBV). Studies subsequently demonstrated that a large proportion of transfusion-associated hepatitis cases were not related to HBV and that other agents were involved, i.e., non-A, non-B hepatitis. Dienstag comprehensively reviews the rapidly expanding information on the epidemiology, clinical features, and experimental transmission of this entity, the search for several non-A, non-B agents, proposed interim screening tests, and the prevention of non-A, non-B hepatitis through reliance on volunteer donors for blood transfusions. This chapter thus provides an authoritative account of a condition that accounts for more than 90% of posttransfusion hepatitis and for approximately 20% of sporadic hepatitis cases.

### HYPERAMYLASEMIA

Hyperamylasemia — increased activity of the enzyme amylase in the serum — has long been recognized as a useful indicator of pancreatic inflammation, despite its lack of precision and specificity. In this detailed review, Berk and Fridhandler describe the limitations of current amylase measurements, the advantages and clinical applications of isoamylase analysis, in addition to other relevant topics, including the ratio of the amylase clearance over the creatinine clearance, the urinary amylase-creatinine ratio, macroamylasemia, and the S-type of hyperamylasemia. The recent advances in this field hold promise of a more reliable assay for pancreatic amylase, with increased clinical usefulness.



## ADAPTATION TO BOWEL RESECTION

Complex functional, metabolic and morphological adaptive changes follow extensive resection of the small intestine—phenomena that are not widely known despite their practical importance. In their definitive study, Urban and Weser review the various metabolic adaptations that follow intestinal resection, involving nutrient absorption, gastrointestinal secretions, mucosal enzymes, intestinal flora and motility and transport. The morphological adaptations discussed include epithelial cell renewal and the role of chalones in the intrinsic regulation of cell renewal. The adaptive responses, and mechanisms of intestinal adaptation include the role of intraluminal nutrients, pancreatic-biliary secretions and the trophic effects of enteric hormones. Increased understanding of the phenomena of intestinal adaptation obviously has important therapeutic applications, as in relation to the intestinal resections for Crohn's disease.

## VASODILATOR THERAPY OF CHF

A reversible increase in systemic vascular pressure as a frequent accompaniment of congestive heart failure is an old clinical observation. The increase was formerly ascribed in large part to an excessive homeostatic attempt to maintain effective arterial blood pressure and volume by retention of salt and water and by vasoconstriction. That the excess of vascular resistance (impedance) thus generated might be purposely reversed with benefit to a ventricle overloaded during ejection (afterload) was a notion developed at a clinical level only in the past decade. Jay Cohn, one of the notable leaders in this field, has written an informative account of the relationship between performance of the heart as a pump and vascular impedance. He has provided helpful suggestions on the specific manipulations of arterial resistance and venous capacitance by vasodilating agents that can be used in the management of the congested circulation that accompanies heart failure.

## NEURAL CONTROL OF THE HEART

The control of the heart as a balance between sympathetic and parasympathetic components of the autonomic nervous system

has been studied extensively in the past, but other neural processes, especially those regarded as serotonergic, are currently receiving a great deal of attention from investigators. One who has been most active in the field is Thomas James, who has provided in his chapter a good deal of old and new information on the nerves of the heart not generally known to most physicians. Although the two types of neuroreceptors—classified on the basis of their dominant response to mechanical stimulation (baroreceptors) or chemical environment (chemoreceptors)—are well known to exist in the aorta and carotid body, their presence in the heart is less commonly known. Of considerable interest is the chemoreceptor in the left main coronary artery, which responds to stimulation by serotonin by a neuroreflex characterized by extreme hypertension. In contrast, serotonin injected in the distal coronary system causes hypotension and bradycardia (Besold-Jarisch reflex). These and other not well known but exciting details of the anatomy and function of the nerves and ganglia of the heart (including the derangements that occur with inflammation or focal degeneration of these neural structures and with cerebral disease), as well as the present medical and surgical management of such derangements provide an informative background in a relatively neglected field that promises in the not too distant future to yield large dividends in clinical applicability.

### SLEEP APNEA SYNDROME

The recognition of 3 normal states of consciousness—wakefulness, sleep with nonrapid eye movements (NREM), and sleep with rapid eye movements (REM)—opened the way to a better understanding of the complex coordination of muscular activity involved in respiration in the three states. Advances in recording the multiple functions involved in respiration during sleep—a form of polygraphy designated as polysomnography—have revealed that pathologic apneas or hypopneas may be categorized into obstructive, diaphragmatic or combined forms. The clinical features of these, the associated alterations in cardiodynamics, the effects of a variety of interventions, the differential diagnosis, and the management make for fascinating reading in the chapter dealing with a group of often-disabling respiratory syndromes occurring during sleep that until recently were more or less ignored at the clinical level.

## TREATMENT OF RENAL CALCULI

At a prestigious national medical meeting many years ago a well-known investigator ended a less than convincing presentation on the treatment of renal calculi by stating that anyone who asked whether stones could be prevented or dissolved asked a pertinent question. Fortunately, progress made since then in the categorization of renal stones and detection and treatment of the metabolic disorders that cause them now invalidate that satirical statement. With the establishment of a protocol for detection of the pathogenesis of renal calculi and with the delineation of precise criteria for the diagnosis of hypercalciuria, hyperuricosuria and hyperoxaluria, an exact classification of patients with nephrolithiasis has become possible. Close upon these advances have come successful methods of management and prevention concisely covered in the impressively quantitative chapter on renal calculi by Drs. Coe and Favus.

## BACTERIAL VARIATION AND ANTIBIOTIC ACTION

The development of antibiotics is now at the level of molecular pharmacology and it is on this level that one can readily understand not only the action of the antibiotic on the bacterium, but the mechanisms by which bacteria develop antibiotic resistance. Dr. Barry Eisenstein's review of these mechanisms from the viewpoint of bacterial genetics and metabolism is presented with an intense awareness of the relevance of each cellular process to the clinical problems caused by the rapid emergence of antibiotic-resistant infections and suprainfections.

## ENDOTOXIC IMMUNITY

The immunology of gram-negative endotoxins has always been a puzzling and difficult clinical and experimental field, replete with eponymic phenomena such as Schwartzman reactions and Waterhouse-Friderichsen syndromes. Dr. Abraham Braude, for many years a student of endotoxin pathophysiology and microbiology, presents for us a lucid review of the way in which immunochemistry has illuminated the study of this field and has led to the isolation of a pure compound ("core" endotoxin) that can be used as an immunogen to provide broad protection against the endotoxic effects of all gram-negative orga-

nisms producing sepsis. The development of core vaccines and antiserum for the prevention and treatment of serious gram-negative infections in human beings now appears to be feasible.

### CYTOMEGALOVIRUS INFECTIONS

It has required the full 25 years since its discovery for us to gain some appreciation of the varied clinical syndromes that can be produced by cytomegalovirus (CMV) infections. A herpesvirus related to Epstein-Barr virus, CMV has several clinical as well as microbiologic features in common with other members of its class. Currently, it is probably the most common congenital infection and seems to follow the human host from cradle to grave. Congenital deafness, heterophil-negative mononucleosis syndrome and Guillain-Barré syndrome have all been related to this ubiquitous human parasite. CMV also rears its head as a prime suspect as a causative agent of demyelinating CNS diseases, inflammatory bowel diseases, granulomatous hepatitis, myocarditis, pericarditis, hemolytic anemia, thrombocytopenias and even some cancers. We must become aware of methods for its detection. Time and careful clinical study will tell whether or not it really causes any or all of the many diseases in search of an infectious agent. Dr. Rome Betts' review should bring you up to date on what clinicians should now know about this sneaky infection.

### DNA ANTIBODIES AND LUPUS NEPHRITIS

Of all the antibodies to cellular antigens discovered during the past 30 years, only those to nuclear antigens appear to be related to the development of lupus nephritis. Moreover, of the many nuclear antigens to which such antibodies have been discovered, only native, double-standard DNA (rather than antigenic determinants on the degraded molecule) seems to have the required physical properties to produce the glomerular lesions of lupus, when combined with its antibodies. Dr. Andrew Chubick reviews this rapidly developing field of clinical immunology and details how sensitive tests currently available (such as the relatively simple immunofluorescence technique for demonstrating antibodies to the native DNA of the flagellate *Crithidia luciliae*) can be applied to diagnosis, prognosis and therapy of patients with the LE syndromes.

## MYASTHENIA GRAVIS AND AUTOIMMUNITY

Myasthenia gravis (MG) has become one of the models of autoimmune disease by the demonstration of a humoral and cellular immune response against the nicotinic acetylcholine receptor (AChR) in striated muscle. An experimental model for MG has been induced by immunization with this acetylcholine receptor, and the interference with normal neuromuscular transmission produced by antibodies to ACh R has been well documented. Dr. John Whitaker reviews in this volume the immunology and pathogenesis of this autoimmune disease. Although the etiology of this disease still remains obscure, our ability to interfere with the specific immunologic injury offers new hope to sufferers of this dangerous myopathic condition.

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