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Editors' Preface

In presenting Volume 23 of Advances in Internal Medicine, the editors, as usual, have grouped the reviews by subspecialty interests but again have emphasized topics, issues and developments about which all internists need to be aware. The essays continue to be in sufficient depth to cover most of the relevant current literature. We persist in believing that continuing education, like any other meaningful education, requires a grasp of the evidence that supports the facts. For such continuing students of internal medicine, this issue, like its predecessors, offers rewarding contributions, which we hope our readers will enjoy as much as did those who edited them.

Gastroenterology

Development of the histamine H_2-receptor antagonists has greatly increased our knowledge of histamine physiology and pharmacology, as well as of gastrointestinal physiology. These compounds, including metiamide and cimetidine, inhibit gastric acid secretion in response to all known secretagogues and they significantly inhibit food-stimulated acid secretion in patients with duodenal ulcer. Feldman and Richardson, in their chapter Histamine H_2-Receptor Antagonists, review this subject authoritatively and meticulously, including the chemistry of H_1- and H_2-receptor antagonists, the impact of H_2-receptor antagonists on histamine physiology, the role and the mechanism of action of histamine on acid secretions, the mechanism of action of H_2-receptor antagonists and the clinical applications of H_2-receptor antagonists, which include the treatment of duodenal ulcer, gastric ulcer, gastritis associated with gastrointestinal bleeding, reflux esophagitis and gastric hypersecretory states such as the Zollinger-Ellison syndrome. Discussion of the toxicology of these compounds involves the bone marrow, thyroid,

kidney, liver, heart and breast. Since H_2-receptors are located throughout the body, these compounds probably will prove useful in other clinical disorders, including neurologic and cardiologic disorders. The text is supplemented by a number of excellent illustrations and the bibliography is the most inclusive to date on this interesting subject.

Breath tests, utilizing stable isotopes, are relatively simple, reliable and safe noninvasive diagnostic procedures now being utilized with increasing frequency in gastroenterology. The two currently popular approaches measure the amount of breath $^{14}CO_2$ after the administration of ^{14}C-labeled compounds and the amount of breath H_2 after the administration of carbohydrate substrates. Breath tests are especially helpful in studies of fat and carbohydrate absorption; e.g., lactose intolerance may be diagnosed by measurement of breath H_2. Breath tests also are important in evaluating ileal function and in the diagnosis of the stagnant loop syndrome. The rate of bile acid deconjugation can be assessed by measuring the excretion of $^{14}CO_2$ after administering a trace dose of cholyl (1-^{14}C) glycine. The aminopyrine breath test provides a semiquantitative assessment of hepatic microsomal function. Two new breath tests involve ^{14}C-labeled xylose and taurine. Other diagnostic applications are in the identification of folate deficiency and in assessing the role of the intestinal microflora in the metabolism of drugs. Hepner, in his definitive chapter Breath Tests in Gastroenterology, clearly summarizes current knowledge in this rapidly developing diagnostic area, supplemented by pertinent illustrations and a very useful bibliography.

Intestinal shunt surgery for the management of extreme obesity dates from the early 1960s. Currently, two procedures are used most widely: (1) a 14-inch by 4-inch end-to-side jejunoileostomy and (2) an end-to-end jejunoileostomy, with the end of the defunctionalized small bowel drained into the cecum or the sigmoid colon. The excellent results are attributable in part to diminished appetite but largely to the reduced absorption of food. Other benefits may accrue, including lowering of an elevated blood pressure and better control of diabetes mellitus. However, a wide variety of medical complications may follow intestinal shunt surgery, including electrolyte depletion, oxaluria with renal stone formation, hyperchloremic acidosis, polyarthritis and severe liver disease. Additional problems include

colonic pseudo-obstruction, pneumatosis intestinalis, increased incidence of cholelithiasis, acute pancreatitis and bypass enteritis. Each of these surgically created, shunt-mediated disorders presents intriguing pathogenetic possibilities. Occasionally, the problems are of sufficient severity as to necessitate the restoration of normal bowel continuity. Reynolds succinctly reviews these medical difficulties following bypass surgery in terms of the possible etiologic mechanisms and updates the most effective treatment currently available for these disorders.

The gastrointestinal mucosa now is recognized as the largest and most complex endocrine structure in the body. Important new developments in our understanding of the physiology and biochemistry of the gastrointestinal hormones have occurred in the past two decades. The best-known hormones, of course, are secretin, gastrin and cholecystokinin-pancreozymin (CCK-PZ). Newer hormones include gastric inhibitory polypeptide (GIP), vasoactive intestinal peptide (VIP) and motilin. Candidate gastrointestinal hormones are numerous and include increton, villikinin, enteroglucagon, gastrozymin, bulbogastrone, chymodenin, entero-oxyntin, pancreoton and pancreatic polypeptide. Chey comprehensively reviews these exciting developments in relation to the secretory and motor functions of the gastrointestinal tract, including intestinal absorption, endocrine secretion, cardiovascular effects and metabolic actions. The trophic actions of gastrin, secretin and CCK-PZ also are reviewed and the roles of gastrin, secretin, CCK-PZ and VIP in various gastrointestinal disorders are summarized in a most informative chapter.

Endocrinology and Metabolism

It now is apparent that the hyperendocrine states can result not only from oversecretion of protein hormones by various endocrine tissues, but that, in addition, such endocrinopathies can result from the abnormal secretion of such hormones by a wide variety of cancers. Doctors Blackman, Rosen and Weintraub have reviewed our current knowledge of the syndromes caused by such ectopic hormone production and have indicated how such syndromes differ from eutopic endocrinopathies. Most important, it is increasingly recognized that the early diagnosis of such ectopic hormonal states is of great practical importance

and frequently can provide the earliest evidence of the presence of a cancer.

It has been widely assumed that diabetic ketoacidosis is characterized by a severe tissue resistance to insulin. In an attempt to compensate for such insulin resistance, it became a routine practice to treat this condition by administering 100–200 units of insulin per hour. As early as 1954, however, evidence began to accumulate that diabetic ketoacidosis might, in fact, respond to much smaller doses of insulin, and with the renewed advocacy of low-dose insulin therapy by Alberti in 1973, this form of treatment became standard practice in many hospitals. Doctor Kitabchi and his colleagues, in their discussion of this rapidly moving subject, review their own well-controlled study comparing low-dose with high-dose insulin treatment of DKA. At a practical level, they draw the important conclusion that low-dose insulin may be as efficacious and far safer than high-dose insulin therapy of the diabetic in ketoacidosis. Perhaps equally important from a pathophysiologic standpoint, these surprising results suggest that we must seriously question the long-held concept that marked insulin resistance is a characteristic of DKA.

Until recent years, the problem of hypophosphatemia was thought to be only rarely of clinical significance. In fact, serious hypophosphatemia now is established as a quite common disorder, especially in the patient population of large city hospitals. Doctor Fitzgerald, in her thorough review of this disorder, emphasizes that with its increasing diagnosis, hypophosphatemia has been found to affect almost every system of the body and can present with such protean manifestations as arthritis, anemia, central nervous system symptoms or simply as severe weakness. Doctor Fitzgerald not only has carefully reviewed the pathophysiology of hypophosphatemia but has provided the clinician with a sound basis for its recognition and early therapy.

Calcitonin is the newest hormone to become available for clinical use. It is appropriate, therefore, that in his extensive discussion of this hormone, Doctor Deftos not only describes the practical therapeutic uses of calcitonin in hypercalcemia and Paget's disease but, in addition, reviews the various clinical states in which abnormalities of calcitonin secretion occur. Perhaps most important, the availability of calcitonin assays has

made it possible to diagnose medullary carcinoma of the thyroid while the disease still is curable. Moreover, the occurrence of this malignant cancer in a large percentage of family members of patients with multiple endocrine neoplasia types 2 and 3 indicates that serum calcitonin levels increasingly will be utilized to detect such tumors.

Circulation, Respiration, Nephrology

Transplantation of kidneys, in addition to restoring patients with previously fatal renal impairment to long (up to 18 years), productive and essentially normal lives, has given rise to a number of new medical, surgical and immunologic problems and to a variety of unfamiliar pathologic lesions in the transplanted kidney itself. It is to the histology of these lesions and their relation to the clinical course of the patient that Hamburger and his colleagues have addressed themselves in their chapter based on their own long and extensive experience with the transplanted kidney.

Although probably 85% of hypertensive patients can be controlled by the so-called stepped-care regimen of therapy, this treatment, really by trial and error, does not appeal to the physician who would like to use therapeutic intervention tailored, if possible, to the pathophysiologic basis of the elevated blood pressure. Enough physiologic and biochemical information now has become available to subdivide essential hypertension into categories or profiles in terms of extracellular fluid volume, cardiodynamics, activity of the sympathetic nervous system and behavior of the renin-angiotensin-aldosterone system. Jay Sullivan has analyzed in detail the significance of these factors in clinical hypertensive states, followed this with evaluation of the "profile" approach to therapy and compared the latter from medical and fiscal viewpoints to the "stepped-care" type of treatment.

The chapter on Hypoventilation: Consequences and Management is partially complementary to the one on Noncardiac Pulmonary Edema in that it emphasizes the differences and variability in ventilatory management of the two conditions. After categorizing the multiple causes of hypoventilation under the headings of intrinsic pulmonary disease, thoracic deformity, decreased ventilatory drive, or combinations, Zwillich, Kryger

and Weil have provided a concise discussion of the clinical and laboratory manifestations; the pathophysiologic consequences on oxygen transport, cardiac output, pulmonary arterial pressure, cerebral blood flow, renal function and hematopoiesis; and, last, management. The chapter will be found most helpful for the rational handling of the commonly encountered clinical problems of acute and chronic hypoventilation.

The old problem of noncardiac pulmonary edema probably received new impetus toward a solution when one form appeared as an acute respiratory distress syndrome in severely wounded soldiers in Vietnam, where it was called "shock lung" or "Da Nang lung." Thanks to both the analytic and integrative efforts of Overland and Severinghaus, the syndrome has begun to assume a comprehensible clinical configuration. It appears to have a uniform pathophysiology, although the precise manner in which exciting and predisposing causes operate still remains uncertain. Among some of the many and increasingly recognized factors that can produce noncardiac pulmonary edema are hypoxia (high altitude), narcotic overdosage, central nervous system trauma or disease, pulmonary microemboli, sepsis and a variety of drugs.

Hematology, Oncology

Over the past decade especially, interest has grown in the effects of agents that handicap platelet functions. It has become well recognized that agents such as aspirin are hazardous in patients with thrombocytopenia or coagulation defects. Less clear is the potential beneficial effect of agents that handicap platelet function in prophylaxis against thromboembolic disease. Many thousands of patients in cooperative studies now are being observed for potential beneficial effects of antiplatelet agents—the most widely used of which are dipyridamole, sulfinpyrizone and aspirin. Among those deeply involved in such studies are Doctors Fuster and Didisheim, who provide a current and critical review of the claims and counterclaims made by many investigators, some of whom have been overly enthusiastic. The fact remains that inhibitors of platelet function are here to stay and better ones probably will be developed, and although more information is needed, the spectrum of their use-

fulness as presently understood should be known to all practicing physicians.

It is a special pleasure to recognize the continuing contributions of Dr. Cecil J. Watson and his colleagues to the field of porphyrin metabolism. These authors present a summary of one of the most exciting advances in recent years in internal medicine—again, most of it related to their own research. Insight into the various biochemical lesions involving abnormal porphyrin metabolism is given as well as dramatic evidence for the manageability of acute intermittent porphyria—a disease often fatal and always frustrating.

Although continuing to be elusive, the role of immune response in both the protection against development of neoplasia and in the clinical evolution of neoplasia remains a subject of intensive research. There now can be no question about the importance of immune responses in neoplasia. Doctors Roubinian and Talal review the highlights of the evidence in a scholarly fashion, one that will be pleasurable reading as well as informative even to the nonimmunologist.

Cancer of the lung continues to rise in incidence and at present causes more deaths than any other form of cancer in the United States. It occurs in many histologic forms and lends itself to staging whereby chances for cure and palliation are improved with more rational use of chemotherapy, radiotherapy and surgery. Doctors Zubrod and Selawry have gained international recognition for their systematic approach to the improved management of lung cancer.

Infection and Immunology

Hepatitis viruses A and B have not yet been cultured in vitro but rapid progress has been made in the refinement and development of serologic techniques by which these clinical and epidemiologic features can be better understood and controlled. In addition, another form of hepatitis has been recognized in which there is no serologic evidence of infection with either hepatitis A or B virus, the so-called non-A, non-B hepatitis. Doctor Barker and his colleagues review current serologic methods for the detection of hepatitis antigens and antibodies that may be important for the recognition and control of viral hepatitis.

During the past 10 years, five chronic human neurologic diseases have been established as *slow infections*—kuru, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis (SSPE), progressive multifocal leukoencephalopathy (PML) and progressive rubella panencephalitis. Although these are rare diseases, their transmission to animals or the recovery of viruses from brains has excited great interest. The implications for the viral etiology of the more common diseases of the central nervous system, such as multiple sclerosis, amyotrophic lateral sclerosis, parkinsonism, chronic focal epilepsy and Alzheimer's disease, are quite clear. For each of these latter diseases there is evidence implicating viruses as a cause. Doctors Johnson and ter Meulen present this evidence and analyze mechanisms by which conventional viruses can establish a virus-host relationship that leads to slowly evolving disease and how unconventional agents (true "slow viruses") may have other properties that may predispose to persistent infection in the central nervous system.

A modern epoch of preventive medicine is the work of The Smallpox Eradication Unit of the World Health Organization. The announcement of the WHO program in 1967 was greeted with skepticism by most epidemiologists and health workers. Now, 10 years later, the apparent eradication of smallpox from all parts of the world is an accepted fact. If not completely eradicated, its existence in any remote corner of the globe now is at least unknown. Furthermore, if smallpox should reappear, one can confidently predict that any outbreak would be promptly wiped out. Dr. Gordon Meiklejohn recounts this dramatic story with the authenticity of his own experience with, and participation in, the program, and its success stands as an example of what can be done when all the countries of the world work together for the betterment of human life.

In 1973, the Food and Drug Administration of the United States in compliance with new legal requirements established panels of experts to help to determine whether currently licensed vaccines produced according to specified standards of potency are both safe and effective for human usage and properly labeled. Your editor of ADVANCES chaired one of these panels concerned with *bacterial vaccines and toxoids* and this panel's review, recently completed, is to be published in the Federal Register. Internists should be intensely aware of the

issues concerning these vaccines, which have greatest relevance to their administration to adults. Some of these issues, ranging from the best established of vaccines, such as tetanus toxoid, to the newest polysaccharide vaccines, such as meningococcus and pneumococcus, are reviewed, and because inadequate attention by internists has been paid recently to the vaccines for bacterial diseases, old and new, this review may be timely.

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PUBLISHER'S NOTE:

The flow chart that appeared on page 239 of ADVANCES IN INTERNAL MEDICINE Volume 21 was based on a chart that was originally published on page 126 of the November, 1971 issue of *Patient Care* (Givens, J., Orentreich, N., and Radcliffe, C.: Helping the woman with unwanted hair). The author, editors and publisher regret that reference to the copyright holder was not included with the reproduction of the chart.

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