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VOLUME 25

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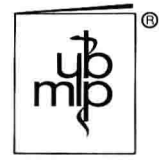

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Editors' Preface

Like its recent predecessors, Volume 25 of ADVANCES IN INTERNAL MEDICINE covers a wide range of developments that should be important to the practice of all internists and, as in previous volumes, there is some difficulty in grouping these broad topics strictly by subspecialty interests. We will, therefore, present a brief editorial comment about each article in the order of its appearance in the volume.

GYNECOMASTIA

Gynecomastia is a frequently encountered yet confusing clinical problem to the internist and a source of major concern to the patient with this condition, yet there have been remarkably few reviews in the literature dealing with this important clinical problem. It is now clear that a variety of commonly used drugs, ranging from digitalis to marijuana, can produce breast development in the male; various tumors can present with this finding; on the other hand, gynecomastia can represent as a benign condition observed in most boys at the time of puberty. In his very scholarly and exhaustive review of this subject, Dr. Wilson summarizes our current knowledge of normal breast development, discusses the hormonal derangements that can lead to gynecomastia and describes the present state of therapy of this condition. This extensive review of the pathophysiology, diagnosis and current therapy of gynecomastia should be of immense help in filling a serious gap in the literature dealing with this important clinical area.

LACTIC ACIDOSIS

Lactic acidosis was only described as a clinical entity in 1961, yet this condition is increasingly being recognized as a serious complication of a number of metabolic disorders. In this volume, Drs. Park and Arieff present a complete and original discussion

of the pathophysiology of this disorder and, in particular, place in context the often overlooked role of the liver in the development of lactic acidosis. New and potentially important therapeutic approaches to the management of lactic acidosis have developed over the last year, making this review particularly timely to the internist who must increasingly recognize this disorder and who, as it now appears, will shortly have available far more effective means of treating it.

Pharmacology of Hormone-Secreting Pituitary Tumors

Until recently it has been assumed that the only two therapeutic approaches to the treatment of the pituitary tumors were surgery and irradiation. Although irradiation and surgery will no doubt remain the mainstays of therapy for pituitary tumors, both of these therapeutic modalities have serious drawbacks. It has recently become apparent that drug therapy may well have a place in controlling the hormonal secretion of functioning pituitary tumors. Specifically, prolactin and growth hormone overproduction can usually be controlled with appropriate medication, and even adrenocorticotropic hormone (ACTH) production by tumors may be modified by pharmaceutical agents. In their review of this rapidly emerging subject, Doctors Vignery and Goldfine present the advantages as well as the limitations of using such agents as Bromocriptine and cyproheptadine in the treatment of acromegaly and of ACTH-secreting tumors. There is now no question that these agents will play an important role in the secondary management and, in a number of instances, even in the primary care of patients with pituitary tumors.

High-Density Lipoproteins

The relation of lipids and of lipoproteins in the pathogenesis of atherosclerosis remains a confusing one. In his review of our current knowledge of high-density lipoproteins, Dr. John Glomset has greatly clarified an important aspect of this field. It now seems very likely that, in contrast to the atherogenic potential of low-density lipoproteins, increased levels of high-density lipoproteins may actually protect against atherosclerosis. Dr. Glomset, one of the pioneers in this field, discusses the factors that are known to regulate serum levels of high-density lipoprotein, how high-density lipoproteins may be deranged in various lipid dis-

orders and, most important, the therapeutic implications of regulating the levels of lipoproteins in possibly preventing atherosclerosis.

Lipoprotein Metabolism in Liver Disease

Dr. Sabesin and his colleagues review the alterations in the plasma levels of lipids and lipoproteins associated with hepatic disease and consider the possible diagnostic applications of the measurements of these levels. The topics include the lipid composition of plasma lipoproteins, clarification of the lipoproteins, ultrastructural aspects of hepatic lipoprotein assembly and secretion, lipoprotein synthesis, metabolism and catabolism, lipid abnormalities in liver disease, and lipoprotein x in cholestatic liver disease. Inasmuch as the liver plays a key role in lipoprotein metabolism and since cholesterol identification and abnormalities in lipoproteins reflect hepatocellular injury or cholestasis, measurements of plasma lipids and lipoproteins are reliable and sensitive indices of hepatic disease.

Cholestasis

Cholestasis refers to a reduction in bile flow. Dr. Javitt reviews the pathophysiology of cholestasis, its clinical recognition, differential diagnosis and the various clinical cholestatic syndromes. These include Byler's syndrome (familial cholestasis), cholestasis of pregnancy and primary biliary cirrhosis. Therapy emphasizes three principles, i.e., relief of the pruritis, prevention of the secondary effects of malabsorption and control of the liver disease, including a brief trial of prednisone and avoidance of foods rich in copper, such as chocolate and nuts.

Management of Acute Pancreatitis

Improved understanding of the pathogenesis of acute pancreatitis and awareness of its impact upon other organs, such as the lungs, heart, kidney and brain, have led to improved treatment of this condition. As Drs. Ettien and Webster emphasize, the approach must be individualized and meticulous. This overview involves 22 separate therapeutic problems, including the role of surgery, the correct diagnosis, treatment of hypovolemia and shock, respiratory insufficiency, infections, calcium and magne-

sium metabolism, renal failure, pancreatic cysts and fistulas, hemorrhage, jaundice and nutrition. This chapter thus provides a comprehensive yet practical approach to a difficult therapeutic problem.

Prostacyclin, Thromboxane and Vasculature

The field of arachidonic acid metabolism, as implied in the preface of the previous volume relative to the article by Drs. Moncada and Vane on the mode of action of aspirin, has continued to progress so swiftly that a follow-up article on the potential vascular effects of the identifiable products of that metabolism seemed indicated. Dr. McGiff, who has been long interested in the interactions between the prostaglandins and the vascular system in health and disease, has written a most provocative summary of where we stand in this area, especially in relation to the biologic balance between vascular prostacyclin and platelet thromboxane. In addition to discussing the biosynthesis, biologic properties and role in vascular function of each of these biologically active compounds and their close chemical relatives, he has gone on to point out how their actions may be modified by drugs and even by the type of unsaturated fatty acids in the diet. The implications relative to the course and possible prevention of the scourge of modern man, atherosclerosis, are intriguing and have already been reinforced by clinical attempts at manipulating the biologic balances involved among the products of the prostaglandin endoperoxides.

The Contact System of Plasma

Over the past 25 years it has become apparent that the different systems of host defense are closely integrated, interrelated and, to some extent, inseparable. When plasma comes in contact with a foreign surface, i.e., any surface except those of vascular endothelium and circulating blood cells, contact-activated phenomena are set in motion. These "intermixed gears" are blood coagulation, fibrinolysis, complement activation and kinin generation. Dr. Saito, from the laboratory that has contributed more information than any other about the contact system, writes a succinct and readily understandable review of the system and its central role in health and disease.

Radionuclides in Cardiology

The rapidly expanding field of nuclear cardiology has been surveyed and summarized in a comprehensive and informative article by Drs. Berger and Zaret. Clinically applicable radionuclide methods discussed include first-pass angiocardiography, gated imaging of myocardial perfusion, the use of infarct-avid tracers and the applications and implications of biologically derived radionuclides. In each category, promising new isotopic methods in various stages of development are also discussed. The whole field is of such diagnostic importance for the detection of abnormalities of myocardial structure and function that all internists must be aware of the advances being made despite the present complexity and cost of the technologies involved.

Cardiac Arrhythmias and Anomalous Atrioventricular Conducting Pathways

The concept of circus rhythm and repeated reentry of an excitatory process into cardiac muscle that has had time to recover excitability was most simply demonstrated in 1913 by Mines in an intact ring of myocardium cut from a fish's atria. Although still not universally accepted as an explanation for clinical atrial flutter, this seems to be definitely the way other excitable tissues, such as "anomalous" pathways, function in rapid heart rhythms; these rhythms were previously ascribed to rapid, repetitive discharge of a focus in the nodal tissues or in the upper or lower cardiac chambers. Although some of the "pathways" have anatomical identity, others are purely functional and become operative only under special circumstances, when the normally present differential properties of refractory period and conductivity of contained "slow" and "fast" fibers are sufficiently dissociated to permit reentry.

The differences in clinically determined antegrade and retrograde conduction and response to drugs of the anomalous pathways make the modern management of arrhythmias more precise and also more complicated. The chapter by Dr. Rosen and his colleagues is an attempt to make the internist aware of new approaches to the management of cardiac arrhythmias that are based on an expanded version of circus rhythm.

Solute Removal in Renal Failure

The limitations of hemodialysis and peritoneal dialysis have stimulated a small group of intrepid investigators to search for other methods of solute removal from the blood of the patient with chronic renal failure. The new methods being tested may be classified as primary, such as hemofiltration and chronic ambulatory peritoneal dialysis, and adjunctive, including the reprocessing of dialysis fluid and the use of orally ingested or hemoperfused sorbents. Drs. Henderson and Sanfelippo have written a summary of the state of the difficult art and science of solute removal which will inform the physician of developing advances in the field.

Hypertension and the Pharmacologic Interruption of the Renin-Angiotensin System

The appearance of a third chapter on hypertension in this series since 1974 attests to the interest and complexity of this ubiquitous clinical problem. In Volume 19, Dr. Muirhead traced the steps leading to the belief of an antihypertensive role of the renal medulla; in Volume 23, Dr. Sullivan reviewed the physiologic and biochemical profiling of the several essential hypertensions relative to therapy. In the present volume, Drs. Hollenberg and Williams have reviewed and weighed the investigative data accumulated by interruption of the renin-angiotensin system achieved by blocking the enzyme that converts angiotensin I to angiotensin II, or by analogue blockade of the receptor sites of angiotensin II in vascular smooth muscle, the adrenals and elsewhere. The article deals in an unusually sophisticated manner with the intricacies and the potential pitfalls of interpretation of the effects of the new biochemical interventions used by them and others to unravel the many stubbornly unyielding pathophysiologic mysteries of essential hypertension.

Pseudogout

The growth of the generic term "crystal deposition diseases" stems from the recognition that both gout and pseudogout are defined by the kind of crystals that are deposited in the joints and cause inflammation, i.e., monosodium urate monohydrate

(MSU) in the case of gout, and calcium pyrophosphate dihydrate (CPPD) in the case of pseudogout. Dr. Daniel McCarty, who identified CPPD as a cause of pseudogout in 1962 and who has since done much to elucidate the full spectrum of the disease, now prefers the term "CPPD crystal deposition disease" because "pseudogout" implies inflammatory arthritis alone, whereas degenerative joint changes due to crystal deposition may often occur, as in gout, without necessarily inducing acute inflammatory changes in every involved joint. Dr. McCarty's review should leave the reader with an appreciation of the surprising incidence of this condition, as well as of the need for more understanding about calcium pyrophosphate metabolism and the general importance of microcrystal deposition in the inflammatory and degenerative joint afflictions.

Cell Markers in Lymphomas and Leukemias

The most notable advance in hematology and oncology in the past few years has been in the ability to identify subpopulations of normal and malignant blood cells, especially among leukemias and lymphomas. These biologic markers are essentially expressions of features of normal cell counterparts and, in many instances, have been found first in the malignant cell population. Drs. Bowman, Melvin and Mauer review the methods used and discuss their value in formulation of diagnosis, treatment and prognosis. Startling and unsuspected differences in each population have been observed, so that the use of cell markers will soon be required in all worthy hematology-oncology programs. Dr. Bowman and his colleagues have provided a clear, current and concise review of advances with which all internists should be familiar.

In Vitro Sensitivity of Cancer Cells

Ideally, the treatment of malignant diseases would involve the use of agents with the same degree of specificity as the clinically useful antibiotics have for bacterial infections, that is, they should be cytotoxic for malignant cells, but relatively sparing of normal tissues. The cure of infectious diseases undoubtedly involves a more decisive role of host defense mechanisms than in malignancies, with the exception of choriocarcinoma of the ges-

tational type. Methods of culture of normal and malignant cells do not equal techniques available in clinical bacteriology. Nonetheless, progress has been sufficient to allow important studies on the sensitivity and resistance in vitro of some human malignant and normal tissues to cancer chemotherapeutic agents and to the screening of some anticancer agents. The status of these genuine and logical advances is well reviewed by Dr. Dow.

"Poisoned Bait" for Macrophages

The monocyte macrophage system (old name: reticuloendothelial system) is especially recognized for its multiple role in host defense, phagocytosis, processing of antigen and influencing cellular and humoral immunoresponses. Thus, it would seem that to handicap this system might be perilous if not outright foolhardy. However, there are certain highly fatal diseases in which overactivity of the monocyte macrophage system plays a critical role. These include idiopathic thrombocytopenic purpura, which is refractory to splenectomy and use of glucocorticoids; its red cell counterpart, idiopathic autoimmunohemolytic anemia; and storage diseases, such as Gaucher's disease and malignancies of cells in the system. For three decades, therefore, efforts have been made to selectively handicap these cells. The first time, through the use of the platelet as a vehicle for transport of cytotoxic agents to macrophages, a "poisoned bait" approach has been successfully used. Selective injury can be inflicted. Drs. Ahn and Harrington review the design and clinical applications of this novel approach.

Group B Streptococcal Infections

Early in this decade, clinicians began to appreciate the growing problem of perinatal infections with group B streptococci – a species erstwhile considered more important in animal infections, notably bovine mastitis – which explains its taxonomic name, *Streptococcus agalactiae*. This organism is now a frequent colonizer of the female genital tract (and hence, of course, passed to males, too) and adult infection has become increasingly commonplace. In the neonate and infant, however, meningitis and serious sepsis due to group B streptococci have become the most common and serious of bacterial infections and some nurseries

are already resorting to routine penicillin prophylactic therapy against these organisms for all newborns. Dr. Carol Baker, a leading authority in this field, provides us with a comprehensive review of the problem, with particular emphasis on the epidemiology and immunology of group B streptococci. Dr. Baker's article includes an intriguing discussion of the prospects for a capsular polysaccharide vaccine made from the type III subspecies, the most serious cause of infant meningitis. This vaccine may be used to immunize pregnant women who are found lacking in naturally acquired type B antibodies. We could thus provide passive immunization for the fetus via transplacental passage of maternal IgG antibody.

Bacterial Adherence

The preferential colonization of various mucosal surfaces by certain strains of bacteria has long been a mysterious phenomenon. Only in recent years has it been recognized that such adherence depends heavily on specific bacterial surface substances that adhere to specific mucosal membrane sites by a ligand-receptor type of interaction with exquisite specificity and very high affinity. Thus, salivary streptococci specifically adhere to the enamel of teeth and cause caries; pharyngeal streptococci adhere to oral mucous membrane cells by a specific surface ligand, lipoteichoic acid, and organisms containing this and other kinds of lipoteichoic acids adhere to cardiac valves and cause endocarditis. Interrelationships between the surface projections of many bacteria (called fimbriae or pili) and cell membrane receptors are under intensive study by many clinical investigators. Drs. Beachey and Ofek, leaders in this field of research and discoverers of the identity of streptococcal lipoteichoic acid as the adherence ligand of group A and other pharyngeal organisms, provide us with a comprehensive and clinically intriguing view of this rapidly moving field. The potential to control bacterial colonization, long a therapeutic dream of many clinicians, may now be achievable.

Appraisal and Reappraisal of Viral Vaccines

Encouraging reports dealing with antiviral chemotherapy and interferon notwithstanding, the greatest opportunities for disease prevention at present and in the immediate future lie with

immunoprophylaxis. But as vaccine use and experience grows, many questions may be expected concerning benefits and risks. To review these issues for each of the widely used viral vaccines, we have secured the services of one of the most authoritative teams in the world, none other than the leadership of the Bureau of Biologics of the Food and Drug Administration of the U.S. Public Health Service. Drs. Harry Meyer, Hope Hopps and Paul Parkman discuss issues common to all viral vaccines and then take up in detail vaccines against smallpox, rabies, yellow fever, influenza, poliomyelitis, measles, mumps, rubella and various combinations of some of the foregoing. The issues are presented with clarity and *Verstand,* an attribute frequently lacking in recent public and professional polemics on the subject.