

Second Edition

DISEASES OF MEDICAL PROGRESS

*A Contemporary Analysis
of Illness Produced by
Drugs and Other Therapeutic
Procedures*

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FOREWORD

In a Foreword to the first (1959) edition of *Diseases of Medical Progress* by Lt. Colonel (then Major) Robert H. Moser, I explained that it had been my privilege in 1956 to attend a USAREUR (U.S. Army Europe) Medical-Surgical Conference at the U.S. Army Hospital, Frankfurt. Of the many excellent and instructive papers delivered during that two-day meeting, I had been most impressed by what Major Moser had to say on "Diseases of Medical Progress." In fact, the material which he presented struck me as so important and timely that I obtained permission to carry home his paper for submittal to the *New England Journal of Medicine*. It was promptly accepted, and appeared in the issue of 27 September 1956.

I then went on to say that it is no secret that certain drugs, surgical procedures, and other forms of therapy can, even when properly employed, create unfavorable, often harassing, and sometime fatal side effects. Unhappily, it is also true (I continued) that drugs are frequently administered or other procedures performed, apparently without due regard for their disquieting and sometimes dangerous potentialities. One need but mention, for example, the wide-spread use of antibiotics for trivial upper respiratory infections and comparable minor ailments—a practice that seems to continue in spite of the exhortations of many qualified authorities that these agents are, as a rule, ineffective in such cases.

Today—some four years later—there is a widening awareness in the medical profession of exactly what Dr. Moser accomplished by his pioneer and thorough survey of the literature of iatrogeny, and of the way in which he crystallized the reported hazards of the many newer agents at our disposal, supplementing his evidence by a large and selective bibliography. The measure of the service which he has rendered to our profession and to the public is in truth the demand for this completely revised and expanded new edition.

As he says in his introduction, the purpose of the present volume is "To foster an attitude of rational caution and to stimulate a spirit of critical evaluation where each physician will ask himself: "Does the possible benefit of this drug outweigh its potential hazard?" Readers of the pages which follow may well come to respect this advice twelve times over since now not one but a baker's dozen of qualified practitioners and investigators have offered, contributed to, and analyzed the evidence.

Not least important is a new chapter of psycho-semantics: "An attempt to express the iatrogenic potentialities of physician-patient relationship." No practicing physician who has close personal rapport with his patients can fail to be aware of how often sick persons have been traumatized emotionally by thoughtless, sometimes by unforgivable, remarks dropped within their hearing or said directly to them. A sharp warning in this area is indeed pertinent.

Last of all, Dr. Moser's rich imagination expressed in the title, *Diseases of Medical Progress* suggests the kinetic stream of proof and reproof, fact and fallacy, action and reaction with which the medical world today perforce must deal. This is a proliferating subject; a vastly important one. I can only repeat again what I wrote in 1959: "One would like to think that this book will find its way to the desk of every physician, and that each will study the pertinent section before initiating, in any one of his patients, a therapeutic measure of whose dangerous potentialities he may not be fully aware." Beyond any doubt many of us will also profit by reading the chapter of psycho-semantics.

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PREFACE TO SECOND EDITION

Diseases of Medical Progress is growing up. In the three years since the original writing⁹ there has been an increasing awareness by physicians throughout the western world of the wonders and hazards of modern therapeutic agents. I do not presume that my few writings^{10,11} and utterances have had anything to do with this therapeutic renaissance, but rather that we have reached a point in medical history when we must reappraise the status of drugs and patients. My writings have been symptomatic rather than etiologic in this trend in western medicine.

Increasing appreciation of the complexities of drug effects has come through many avenues of investigation. The wedding of the percutaneous biopsy and improved light and electron microscopic techniques has permitted dramatic insight into the wonders of intracellular morphology and physiology. We are now able to observe the specific action of drugs within the cell (i.e., cholestatics in the hepatic parenchymal cell).

Therapeutic agents are carried in the blood and body fluids to effect all cells of the organism. However, such effects become clinically perceptible only when the function of certain organs is compromised to the point of producing signs and symptoms. It is by these phenomena that we have learned to characterize drug toxicity. Effects upon the other cells of the organism are not immediately evident but subtle influences may be operative that become manifested clinically at a later period. Such long range effects may never be correlated with antecedent administration of a specific drug. The influence of drugs administered to the parturient mother upon the neonate remains an area that is virtually unexplored. Beyond this, the knowledge of drug effects upon germ plasma and unborn generations is even more mystic.

There is reasonable evidence derived from isotopes and fluorescent tagging techniques that certain drugs may act as haptens to join disease-damaged (or normal) protein or subprotein sub-

stances to form an antigen that will provoke antibody formation. This alien unit may then influence function and/or structure of the parent organ. The antigen-antibody unit may travel via the blood to a distant organ and exert a hostile influence at that site.

In another area, there is little known of the role played by drugs in predisposing an organ to attack by a micro-organism or degenerative process (i.e., corticosteroids in pulmonary tuberculosis and osteoporosis or phenacetin in interstitial nephropathy). One could ask, what is known of the effects of drugs upon an organ that is already diseased—with limited capability to metabolize, detoxify and otherwise cope with “therapeutic” agents (i.e., the damaged liver and chlorpromazine or phenylbutazone)?

“Drug residuals” was the subject of an editorial in a leading journal.³ Reserpine was found to exert an influence several weeks after it had been discontinued. Also, Shapiro¹⁵ discovered that protein bound iodine levels in the sera of women who had received iophenoxic acid remained elevated six to seven years following exposure to the drug; offspring of these mothers born several years after the maternal ingestion of the iophenoxic acid also had extremely high protein bound iodine levels. Apparently this property is not found in iopanoic acid which differs from iophenoxic acid only by an amino group which replaces a hydroxyl on the benzene ring.

We are still plagued by the difficulty in obtaining data on incidence figures for unanticipated drug effects. We are aware that most of these reactions are rare, but we have few ideas of degree on the basis of isolated case reports or small series.

One wonders how much we really know of drug metabolism and excretion—how much of our knowledge is inferential and perhaps incorrect? What are the residual effects of prolonged exposure to alien substances, long since assumed to be detoxified and gone—yet lingering in unsampled tissue reservoirs?

The world literature on this general theme has expanded so rapidly that I have called upon a dozen of my friends, representing various subspecialties to help me patrol the literature and

write this second edition. These men are experts in their respective fields, and we share a mutual enthusiasm in the crusade to encourage rationality in drug therapy.

It is inevitable in a book of this nature written by many authors that some reduplication of subject matter will occur. This aspect was edited with some relaxation; an effort was made to avoid painful redundancy while attempting to preserve the integrity of the individual chapter. We can rationalize by saying that some repetition serves a pedagogical function. I feel the variations in literary style and organization from section to section add a degree of charm, while the basic philosophy of the book is generally preserved.

The writing was undertaken in many different areas under unusual circumstances. Dr. O'Neil Barrett wrote his section while on duty in South Viet Nam utilizing library facilities at Madigan and Tripler General Hospitals. Others had problems of lesser magnitude; no one had "sufficient" time. The interval from the arbitrary cut-off date for reviewing journals until publication was a frantic period. To read, abstract, write, rewrite, edit, rewrite, and then index, in an effort to offer a book to the medical public which is extremely current (in medical time) was a challenge.

I hope we have achieved this goal.

Our foreword has again been written by friend and scholar, Dr. Dennette Adams. As in previous publications our concern is with "diseases-which-would-not-have-occurred-if-sound-therapeutic-procedure-had-not-been-employed." The phenomenon of a second disease emerging *de novo*, as we treat for the original process is a traditional nemesis of the practicing physician.

The problems besetting the physician are complex. Social, economic and professional pressures combine to influence the practice of medicine. The busy practitioner is besieged by literature and attractive hand-outs extolling the virtues of new drugs. His patients are appraised of "miracle medicine" in the lay journals and newspapers well in advance of their publication in medical periodicals. The physician has little time to analyze clinical trials of new drugs even when they are eventually published.

Consequently he finds himself quite often in the anomalous position of preparing to prescribe a new drug of unproven value and unknown toxicity.

The problem of appraising the current situation and discussing mechanisms of adverse drug effects is admirably discussed in papers by Friend⁴ and Hoskins, Modell,^{6,7,8} Prickman,^{12,13} and Samter and Berryman.¹⁴ In essence, the latter authors state, "The relative infrequency with which drug reactions are encountered is a tribute to the resourcefulness of the body." But parenthetically it may be added that it is not fanciful to suggest that for every drug there will be one or more patients who may react with unpredicted and adverse consequences.

Realization of the problem throughout the profession can be attested by the increasing number of publications having to do with iatrogenic disease.^{1,5,17} Scarcely an issue of any journal will appear without at least one article devoted to untoward effects of drugs or surgical procedures. In the August 22, 1959 issue of the J.A.M.A., eight of the twelve papers discussed "diseases of medical progress." *The Journal of the Albert Einstein Medical Center* devoted its entire October 1959 issue to the subject.¹⁶ The Anesthesia Study Committee of the New York State Society of Anesthesiologists presented thirty-eight topics on iatrogenic problems which appeared in each issue of the *New York State Journal of Medicine* from January 1956 until December 1957.² These analytical articles were devoted to untoward effects of drug and procedures, and countermeasures. Reprint services^{1,17} and books⁵ designed to keep physicians posted on new drugs and drug-induced diseases have appeared. For the past year, I have been abstracting articles which appear in the "Diseases of Medical Progress" section of *Clinical Pharmacology and Therapeutics*. Medical meetings throughout the country have had panels and papers on "drug-induced" diseases. Finally the Council on Drugs of the American Medical Association is taking decisive steps to expand the Committee on Reporting Blood Dyscrasias. It is hoped this action will culminate in a comprehensive registry to facilitate reporting of unanticipated

effects of drugs by physicians in every area of medicine. It is a bold step forward.

Our purpose is to foster an attitude of rational caution and to stimulate a spirit of critical evaluation where each physician will ask himself "Does the possible benefit of this drug outweigh its potential hazard?" Our book is intended to be a ready reference for the physician who proposes to use a drug which he has not employed previously. We have attempted to record "diseases of medical progress" which were detected through reviewing medical literature. There is little doubt that we have missed many, especially those reported in foreign language journals. It is also unfortunate that many important untoward drug reactions are observed which do not find their way into the medical literature. We look hopefully to the implementation of the AMA registry on adverse drug effects to correct this situation.

We have attempted to keep the book simple and readable. A new chapter on "Psycho-semantics" has been added. This is an attempt to express the iatrogenic potentialities of physician-patient relationship. We hope you will find the index adequate and the references ample. We have utilized both generic and trade names to facilitate recognition of drugs.

ROBERT H. MOSER

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PREFACE TO FIRST EDITION

The somewhat curious nature of this subject—Diseases of Medical Progress—would seem to warrant a word of explanation regarding its origin and evolution. In 1955, while serving as Chief, Department of Medicine in the small U.S. Army Hospital on the outskirts of Salzburg, Austria, I had a rather singular medical experience. During routine daily rounds, my ward officers presented three patients in sequence, each with widely divergent syndromes, yet with a single striking factor that was common to all.

The first lady was an asymptomatic, but deeply jaundiced housewife who had been taking chlorpromazine for a mild depression. The second was a husky sergeant who had been placed on token doses of quinidine to arrest annoying supraventricular premature contractions. He had developed a severe thrombocytopenia. The last was an elderly hypertensive gentleman who had been placed on reserpine and subsequently developed a distinct parkinsonian tremor. In each instance the syndrome had been induced by rational, widely accepted therapy which had been properly ordered and accurately administered.

That evening I turned to my current literature file just to see how many publications relating to similar "iatrogenic" illnesses could be gathered in a casual perusal. In the space of one hour, forty acceptable papers were lying on the desk. This aroused my curiosity and I began to collect articles that appeared in the current literature. I pursued this new "hobby" for a few months, organized it into a somewhat rambling paper, and presented it to the USAREUR (United State Army—Europe) Medical-Surgical Conference in Frankfurt-am-Main, Germany on March 17, 1956. By good fortune, Dr. F. Dennette Adams of Boston, who had been touring the military hospitals as the Surgeon General's Consultant in Internal Medicine, was seated in the audience. He was very kind and expressed interest in the subject. He also suggested that it might be worthwhile to publish. As a result, a re-

vised and amplified version subsequently appeared in the Medical Progress section of the *New England Journal of Medicine* (September 27, 1956).

The reprint response and general comment in letters from physicians was encouraging to the extent that I continued to earmark the file "DMP" articles that turned up in the course of my reading of the medical literature. The present monograph is the final compilation of the data accumulated from journals and abstracts which crossed my desk from 1956 to late 1958. Certainly this is not an attempt at a comprehensive literature review, but rather is a sampling of the material that the average Internist would have occasion to see.

The index and bibliography may seem disproportionately large when compared to the text. The index is designed to permit rapid location of information of a specific nature amid the broad spectrum of drugs, procedures and induced diseases. The bibliography is imperative to enable physicians who are interested in finite areas to amplify their knowledge by more detailed perusal of case histories and their correlative discussion. In many instances I have alluded briefly to an entity which should be studied in greater detail by the interested physician.

I feel that the subject of induced disease should be one of continuing and dynamic interest to all practitioners of medicine. It is mandatory that we continue to be alert to the subtle hazards of each drug and procedure we employ, since we are adequately propagandized regarding the apparent and well-publicized benefits. We must be prepared to assume the great responsibility that attends the remarkable therapeutic armamentarium now at our command.

I wish to express my deep gratitude to Miss Sue Bond, whose patience and forbearance in typing the many revisions and additions of this manuscript have been of inestimable aid.

RHM

San Antonio, Texas

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RHM

CONTENTS

FOREWORD— <i>F. Dennette Adams</i>	Page ix
PREFACE TO SECOND EDITION	xi
PREFACE TO FIRST EDITION	xvii

Chapter

I.	ANTIBIOTIC-INDUCED DISEASES— <i>Thomas J. Smith</i>	3
	Introduction	3
	The Problem of Resistant Bacteria	4
	Chemoprophylaxis	7
	Diseases due to Resistant Staphylococci	9
	Diseases due to Gram-negative Bacilli	14
	Fungal Infections	16
	Antibiotics	17
	Penicillin	17
	Penicillinase	23
	Streptomycin and Dihydrostreptomycin	23
	Tetracyclines	25
	Erythromycin, Erythromycin Propionate and Lauryl Sulfate	27
	Oleandomycin and Triacetyloleandomycin	28
	Chloramphenicol	29
	Novobiocin	31
	Vancomycin	32
	Ristocetin	33
	Kanamycin	33
	Neomycin	34
	Colistin	34
	Amphotericin B	35
	Griseofulvin	36
	Other Antibacterial Compounds	36
	Sulfonamides	36
	Sulfamethoxypyridazine	38
	Sulfadimethoxine	38
	Nitrofurantoin	38
	Furaktadone	39
II.	CARDIAC AND VASCULAR DISEASES— <i>Robert H. Moser</i>	61
	Cardiac Diseases	61

<i>Chapter</i>	<i>Page</i>
Rhythm Disturbances	61
Digitalis and Diuretics	61
Quinidine and Procaine Amide	67
Rauwolfia Drugs	67
Vasopressor Drugs	68
Thyroid and Anti-thyroid Drugs	70
Hyperkalemia	71
Magnesium	71
pH Alterations	72
Other Drugs	72
Papaverine	72
Caffeine	72
Nicotine	72
Meperidine	73
Veratrum Preparations	73
Methylphenidate	73
Suxamethonium	73
Anesthetic Agents	74
Hemorrhagic Diatheses	75
"Syndromes-at-Large"	76
Anticoagulants and the Central Nervous System ..	79
Tests for Anticoagulant Effect	80
Rebound Hypercoagulability	82
Enzyme Systems	82
Diseases of the Myocardium	83
Pericarditis	86
Myocardial Trauma	87
Salicylates and Rheumatic Fever	87
Rebound in Acute Rheumatic Fever	88
Cholesterol-lowering Agents	88
Vascular Diseases	90
Hypertension	90
Hypotension	90
Peripheral Vascular Diseases	90
Anti-hypertensive Agents	91
III. COLLAGEN AND COLLAGEN-LIKE DISEASES— <i>Robert H. Moser</i>	100
Urticaria and Anaphylaxis (Capillaritis)	100
Arteritis	101
Lupus Erythematosus-like Syndromes	101
Summary Chart	104
IV. DERMATOLOGIC DISEASES— <i>John S. Ferguson</i>	108
V. HEMATOLOGIC DISEASES— <i>O'Neill Barrett</i>	118

Chapter	Page
Total Bone Marrow Suppression	119
Agents which Usually Produce Bone Marrow Suppression if Sufficient Dose is Given	119
Agents which Occasionally Produce Bone Marrow Suppression	120
Antimicrobial Agents	120
Anticonvulsants	121
Anti-thyroid Drugs	121
Antihistamines	121
Miscellaneous Agents	121
Erythrocyte Abnormalities	122
Anemia	122
Bone Marrow (Erythroid) Hypoplasia	122
Hemolytic Anemia	122
Megaloblastic Anemia	125
Antimetabolites	125
Anticonvulsants	125
Pernicious Anemia	125
Anemias Following Surgery	125
Miscellaneous Anemias	126
Abnormal Hemoglobin Formation	127
Methemoglobinemia	127
Sulfhemoglobinemia	127
Leukocyte Abnormalities	127
Leukopenia	127
Granulocytopenia	127
Lymphopenia	129
Leukocytosis	130
Platelet Abnormalities and Thrombocytopenic Purpura	130
Coagulation Abnormalities and Non-Thrombocytopenic Purpura	133
Complications of Blood Transfusion Therapy	136
Miscellaneous Conditions Relating to the Hemopoietic System	140
VI. HEPATIC AND GASTROINTESTINAL DISEASES— <i>Norman M. Scott</i>	155
Hepatotoxic Drugs	156
Cholestasis	156
Hepatocellular Necrosis	161
Miscellaneous Hepatotoxins	163
Hepatic Coma	166
Serum Hepatitis	167