GOUT
and URIC ACID METABOLISM

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With a Chapter on

INTERMEDIARY PURINE METABOLISM

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Dedication

Dedicating this Book in honor of the late Dr. Alexander B. Gutman, Ph.D., M.D., is a source of great pleasure and satisfaction to each of us. Dr. Gutman had a searching and critical intellect. He was an excellent scholar, an outstanding investigator, an inspiring teacher, a true Old World Humanist and at all times a kindly, gentle individual held in great esteem by all who knew him. The logic of his inquiring mind and knowledge gained by his investigations in Clinical Gout and Uric Acid Metabolism are evident throughout this book.

Preface I

Although my deep interest in the clinical and metabolic problems of gout has been sustained for more than four decades, the systematic pursuit of achievable goals has been interrupted periodically and impaired seriously a few times by varied diversions, particularly peripatetic assignments and major editorial activities. Neither of these is conducive to the accumulation of a large series of patients and their long-term followup.

This deficiency has been amply corrected in the preparation of this book, plus the complement of many unanticipated benefits, by the enlistment of help from Dr. Ts'ai-fan Yü, the full-time associate of Dr. Alexander B. Gutman for more than 25 years. Through their efforts, 1800 fully documented cases of gout have been assembled and carefully followed. This composite is the largest series of patients with gout with regular and detailed sequential studies in this country or possibly anywhere in the world.

The many contributions of the unique team of Gutman and Yü include several that are epoch making. The early use of labeled precursors of uric acid demonstrating the undue enrichment of uric acid nitrogen and the deficient excretion of ammonia led to the suggestion that a diversion of glutamine from renal production of ammonia to de novo uric acid synthesis occurred. The pharmacologic actions of several new and old antigout drugs, and particularly the paradoxic action of salicylate upon the renal excretion of uric acid, had practical clinical applications in the precise management of the gouty patients. Another contribution of the team was the development of the theory of simultaneous renal tubular reabsorption and secretion of uric acid in man, as had been demonstrated in lower animals.

The accomplishments of this unique team are legion, and have deeply enriched the medical literature, but a volume such as this never appeared, even though I had subconsciously expected such a tome for a number of years. The untimely death of Dr. Gutman seemed to end the possibility. Almost a year after Dr. Gutman's death, I felt it proper to suggest an editorial alliance with Dr. Yü. After more than the usual period of deliberation, and I am sure soul searching as to what Dr. Gutman would have wished, she assented. The opportunity to explore and exploit the rich mine on the sixth floor of the old wing of the Mount Sinai Hospital, known to many as the "Gout Research" complex, has been a rewarding experience for me during the past two years.

Dr. Yü has been a co-author in every way. The venture began with the planning of the Table of Contents. It was her suggestion that a new approach to organization be taken, one quite different from previous editions. The concordance continued with the review of each draft of each chapter of the manuscript, and concluded with a line by line critique. Each accepted the challenge to review the other's composition. Thus this book is more than a series of separate chapters. The exception is the chapter on Intermediary Purine Metabolism and Its Regulation, prepared by one of the most qualified workers in the field, Dr. J. E. Seegmiller of the University of California School of Medicine at San Diego.

I am indebted to several staff members at the University of Miami School of Medicine. Dr. Azorides R. Morales, Chairman of the Pathology Department, was of great help in the preparation of the Pathophysiology chapters. Dr. Philip J. Hodes of the Radiology Department helped screen and choose all of the roentgenograms of the bones and joints. With but few exceptions, the cases were selected from Gutman and Yü's series of the 1,800 patients at the Mount Sinai Hospital. The x-rays of the differential diagnosis of joints were selected from the Radiology Department of the University of Miami School of Medicine. The members of the Arthritis Division, Dr. David S. Howell, the Director, and his associates, Drs. Harvey E. Brown, Norman L. Gottlieb and Roy D. Altman, were constantly on the alert for the usual and unusual cases of gout or those suggestive of gout throughout my tour of duty in the Arthritis Clinics at the Miami Veterans Administration Hospital and Jackson Memorial Hospital.

The authors are indebted to Mrs. Beatriz Gonzalez and Ms. Emma Vignau for the excellence of the line drawings and to Ms. Diane Simonoff, Mrs. Marjorie S. King and Mr. Charles M. Bailey for the preparation of the black and white prints, each from the Department of Biomedical Communications.

Beyond the Medical School orbit, continuing financial support has come from Maxine and Paul Frohring and Polly and Lawrence E. Connelly, Jr., loyal supporters of the Calder Memorial Medical Library at the University of Miami School of Medicine. It is a fine source Library and each member of the Reference Staff has been of great help in the search and retrieval of many of the cited and uncited references. And latterly, the Arthritis Division has been enriched by a fine bequest for Arthritis Research from an anonymous donor.

John H. Talbott, M.D.
Key Biscayne, Florida

Preface II

The studies of the pathogenesis and management of gout in the last quarter century embraced the primary research efforts of Dr. Alexander B. Gutman and myself. My association with Dr. Gutman and the study of Gout and Uric Acid Metabolism began at the College of Physicians and Surgeons, Columbia University, New York, in 1947. The work was later transferred and continued at Mount Sinai Hospital, in the same city, when Dr. Gutman became Chief of Medicine in 1951 (holding this post until 1968). During these years, we explored the nature of the metabolic errors in gout, the mechanism of renal tubular excretion of uric acid, the metabolic pathways of drugs and their interactions, and the possible role of glutamine and glutamate in the genesis of hyperuricemia. The introduction of protracted uricosuric therapy leading to the disappearance of tophi ushered in a new era in the management of gout. This convinced us that investigative studies and clinical management were inseparable. The many new developments in gout research were one of the major reasons why the long conceived book on gout never materialized, although many of our studies were published in various medical journals periodically.

The paths of Drs. Alexander B. Gutman and John H. Talbott, which involved surprisingly parallel careers, crossed first in 1929 at the Presbyterian Hospital in the City of New York, the clinical arm of the above noted College of Physicians and Surgeons. Dr. Gutman's initial interests were of metabolic bone diseases, alkaline and acid phosphatases, and multiple myeloma proteins. A decade later, he became interested in gout. On the other hand, Dr. Talbott began his studies on gout at the Massachusetts General Hospital in Boston shortly after he left the Presbyterian Hospital in 1931. Dr. Talbott in turn became Chairman of the Department of Medicine at the School of Medicine, University of Buffalo, 1946-1958, followed by the post of Editor-in Chief of The Journal of the American Medical Association, 1958-1970. Dr. Gutman founded the American Journal of Medicine in 1946 and remained as Editor-in-Chief until 1971. Dr. Gutman was Chairman of the Department of Medicine at Mount Sinai, 1951-1968, which became Mount Sinai School of Medicine of the City University of New York. Subsequently he was appointed Distinguished Service Professor of Medicine.

Realizing that Drs. Gutman and Talbott had comparable research interests and almost identical professional goals, I accepted the latter's invitation to be a co-author of this book on Uric Acid Metabolism and Gout, some time after Dr. Gutman's untimely death, May 4, 1973. The partnership has been exceedingly congenial, with a modicum of controversy if any.

Special mention should be made of the continued support since 1951 from the National Institute of Arthritis, Metabolic and Digestive Diseases, National Institutes of Health. The unique support from many friends with gout, their active participation in various studies, and their generous financial aid are greatly appreciated.

I am greatly indebted also to Dr. Lawrence Berger for his untiring help in the studies of renal excretion of uric acid, to Drs. John J. Burns, Peter G. Dayton and James M.

Perel in unfolding the study of drug metabolism and interactions, to Dr. M. Earle Balis in collaborative enzyme studies, to Dr. John Roboz in the development of highly skillful technics, to Mrs. Clara Kaung for her meticulous technical assistance, to Mr. David Cope for the data processing, Miss Ruth Zia for help in data analyses, to Mr. Herman Gold, supervisor proofreading department of *The New York Times,* and advice from my colleagues and friends, too many to be mentioned specifically.

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Contents

I

History

Among a number of references to the history of gout, several are especially noteworthy. Delpeuch's large volume on the *History of Gout and Rheumatism* [212] published in 1900 was followed more than half a century later by Copeman's small monograph on the *History of Gout and Arthritis* [182]. In the interim, shorter contributions largely restricted to gout, were made by the Grahams [347], Bywaters [143] and Rodnan [727].

Although the earliest clinical description of gout naturally is attributed to Hippocrates (460-370 BC) [419], gout may have been the disease intended in some earlier writings. Greek mythology includes several figures who were affected with what may have been gout, and Egyptian archeology contains several items concerning the ravages of the disease or herbs used in treatment.

Stukeley in 1734 referred to gout in biblical scriptures, in Greek mythology, and in the Greek drama by Lucian called *Tragopodagra* [859].

"As to the history of the distemper, I need observe no more than that the earliest account we have of it is in the Scripture and the earliest we can expect to have. 'II. Chron. XV 12. And Asa in the thirty and ninth year of his reign was diseased in his feet, until his disease was exceeding great: yet in his disease he sought not to the Lord, but to the physicians. And Asa slept with his fathers and died in the one and fortieth year of his reign. –It can't be doubted that this distemper was the gout.–I don't suppose Asa was the first that had this distemper, but is the first recorded in history and this is near 200 years before the foundation of Rome."

Stukeley assumed that several Greek leaders in the Trojan War suffered from gout, including Priam, Achilles, Oedipus, Protesilaus, Ulysses, Bellerophon, Plesthenes and Philoctetes as well as Tyrannion the grammarian, who died of gout.

And in Lucian's *Tragopodagra*:

"from hands and feets extremitys
th' impetuous fiery ichor flyes;
a furious spirit thro' every vein.
rushes with unrelentive pain.
whilst every member, as it come,
th' encaustic pestilence consumes
as the rock Aetna's furnace burns,
and marble into pumice turns:
so by thy chemistry we find
our bones and joints to chalk calcin'd;
or knotty made and motionless
O who can thy dire dills express!"

There are three artifacts in Egyptian archeology worthy of note. Smith and Jones discovered a large mass in the great toe of the skeleton of an elderly male in a cemetery in Upper Egypt [805]. Urates in the deposit were identified by chemical

analysis. The oldest renal calculus in current collections, recovered also from an Egyptian mummy of at least 7000 years ago, contains a uric acid nucleus [501]. The finding of a urate calculus does not prove that gout was responsible, although the chances are 10-20 to 1 in favor of such an inference. A third item in Egyptian archaeology, dating from 1500 BC, is the several prescriptions deciphered in the Ebers papyrus; these included crocus and saffron herbs, from which colchicum is derived. Since colchicum is the only recognized specific anti-arthritic agent in ancient therapeutics, it is possible that the preparations containing this active principle were used in the treatment of gouty arthritis. Ghalioungui, in reviewing descriptions of rheumatic disorders in the ancient Egyptian papyri, could find no clear description of gout, although in two cases, Eber's papyrus, Nos. 620 and 621, arthritis in the toe was mentioned [326].

Hippocrates probably identified gout as distinguished from rheumatic fever, and among his surviving *aphorisms*, three are pertinent to gout and gouty arthritis, a disease attributed by him to an excessive accumulation of phlegm, one of the body humours, which disturbed the affected joints causing acute pain [419].

"Firstly. Eunuchs do not take the gout, nor become bald.

"Secondly. A woman does not take the gout unless her menses have stopped.

"Thirdly. A young man does not take the gout until he indulges in coitus."

The low incidence of gout in females and especially in menstruating females continues into current practice. And if we accept the fact of coition as capacity for intercourse and impregnation, most males suffer their initial attacks after puberty.

In his *Affection of the Parts*, Hippocrates stated that "Podagra is the most potent of all joint affections, it lasts long and becomes chronic . . . . The pain may become fixed in the great toes . . . it is not fatal [419]." Hippocrates believed in the value of diet in management and although he espoused the concept which persisted for many centuries that gout was associated with rich foods, debauchery and bacchus, he allowed wines in some patients with gout, especially in the elderly.

Gout scarcely lost its prominence in medicine until early in this century, when it receded temporarily. Several factors are responsible for its relatively persistent prominence. These include its ready identification with the soma—the joints, its hereditary nature, first noted by Aretaeus the Cappodocian (2nd Century AD), its sometime association with renal stones and the frequency of subcutaneous urate tophi [18]. Each of these items may be self-evident to the laity as well as to the physician.

Since Rome was the center of the Mediterranean world in the early centuries of the Christian era, most references to gout are associated with those who came from Asia Minor or Greece to visit Rome or who were citizens of the Roman Empire. Celsus (25 BC-50 AD) was not a physician but a well bred country gentleman who composed an eight volume encyclopedia, *De re Medicina* [160]. In the management of arthritis (including podagra) he stressed the value of regular exercise and avoidance of obesity, noted the familial tendency and observed that most of the Roman emperors had suffered from gout. The consul Agrippa eventually committed suicide because of the excessive pain from recurring attacks of acute gout. Among the litterateurs of the Roman Empire, Virgil, Martial, Pliny, Seneca and Ovid referred to gout in their writings, the latter noting that a cure was not possible. Sorranus of Ephesus (98-138 AD), his senior colleague Rufus and, above all, Galen (130-200 AD), from Asia Minor, left a fine heritage on the subject of gout [314].

Galen was probably the greatest scholar and clinician after Hippocrates, whom he admired and emulated. He also attributed gout to an accumulation of humours [314]. He stressed the importance of diet and allowed some wine. Aretaeus (135 AD), noted the higher incidence in males and suggested that the cause of gout was a toxic substance, a *peccant humour*, rather than the accumulation of one of the natural humours [18]. He was one of the first to mention hellebore, a mild purge, as embodying some ingredient specific for gout. Since for centuries purging was common treatment for many conditions, it is not surprising that some concoctions containing hellebore, as well as hermodactyl, a close relative of *Colchicum autumnale* (Fig. 1), were given without appreciating that gouty patients might have responded to the colchicum alone, minus the nonspecific action of the purge. The value of hellebore and hermodactyl in gout is mentioned over many centuries; even after the discovery of the specific value of colchicum in the 6th Century AD, it competed favorably with this related herb.

After the fall of the Roman Empire in the 4th Century AD, medicine moved to Byzantium, now Istanbul, where traditional concepts prevailed. Exceptions were Aetus (4th Century), who recommended lodestones (magnets) for relief of pain in the joints; Paul of Aegina (625-690 AD), who attributed anxiety and passions of the mind as sometime precipitating factors in gout; and Alexander of Tralles (525-605 AD), whose brother gained architectural glory as the designer of the great church of Hagia Sophia

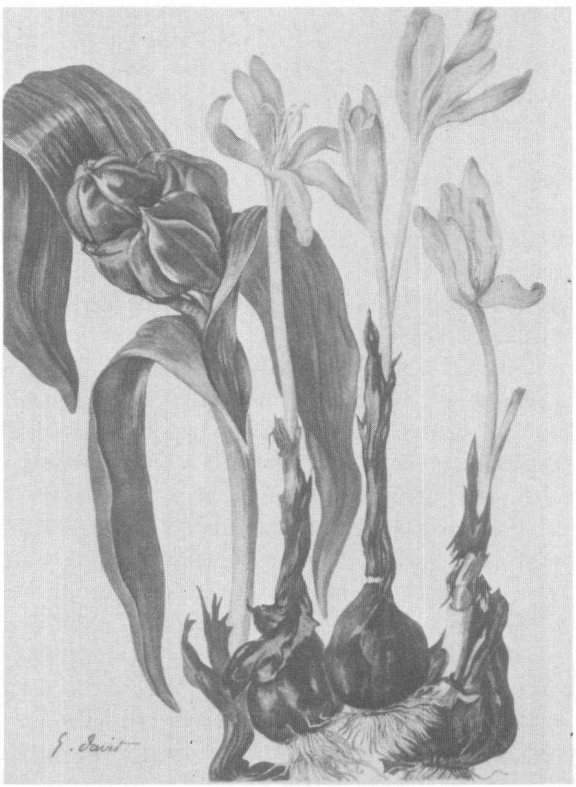

FIG. 1. Autumn Crocus–*Colchicum autumnale*.

in then Constantinople, introduced colchicum (hermodactyl) into the management of gout [212, 695]. This observation makes it (colchicine) the first specific in the practice of medicine, which specificity remains. Colchicum had been described by Dioscorides earlier (ca AD 54-68) but not for the management of gout [221].

Alexander, as well as Paul, expressed some misgivings concerning the drastic purgative effect of colchicum and, in their search for a less violent agent (unintentionally not endowed with anti-gout property), may have contributed to the loss of prestige of colchicum in clinical medicine for several centuries, dark ages for gout and colchicum. Another explanation for the fall from favor of colchicum was the lack of quantitation of dosage. The pure alkaloid, colchicine, has a narrow margin of safety between the amount needed to relieve acute symptoms and its undesirable purgative action, the cure in some cases of gout without quantitation being worse than the disease. Not until the 13th Century was colchicum restored to pharmacognosy.

A report by Viets of this era is pertinent [907]:

"A famous book on gout, Liber de Podagra, et id Genus Morbis (Paris, Guil, Morelium, 1558) by Demitri Pepagomeni. Written before 1282, considers gout as a constitutional disease caused by incomplete elimination of excrets. Demetrius therefore, treated his patients by purgation, using a pill of aloes.

"Gout:—the words, gout and podagra, became interchangeable about the time that Demetrius wrote his book. The Oxford English Dictionary notes, as of 1920.

'In his fot ane hote goute, that poudagre idcopcod is.'

"and by 1300.

'The gutte the potagre es it to bete,
If fell al dun in-til his fete.'

"—Neuwirth points out that although Ralph Bocking (Radulphus) is credited with first using the term, gutta, in his biography of St. Richard of Wyche, Bishop of Chichester, composed about 1270, Villchardouin, writing between 1207 and 1212, used the words, une grant maladie de gote, and gutta is traced to the tenth century."

In an account of the last Crusade (1270) one of the leaders fell sick in Jerusalem of a "gote" in his knees and feet, while sufferers with "gutta" were among those miraculously cured at the tomb of St. Thomas à Becket in Canterbury in the same period. In the first English textbook of Medicine, written in 1280 by John of Gaddesden, physician to King Henry V of England, he observed that in the hereditary transmission of gout, such descent is more apt to be through the mother.

Gilbertus Anglicus in the 13th Century named a colchicum preparation "Cothopcie Alexanderine," in honor of its discoverer seven centuries earlier. He described tophaceous gout but did not identify the herb with gouty arthritis. Thus, colchicum as a specific for gout remained in relative oblivion until its rediscovery by Professor Baron Von Stoerk, student of Boerhaave, physician to Empress Maria Theresa and chief of the medical clinic in Vienna. He established, by experimental procedures, the safety of small doses for dropsy and therefore its safety for gouty arthritis as well. But the great event was the success enjoyed throughout Europe by Husson's patent medicine. L'Eau d'Husson was available as an over-the-counter preparation in 1780. The active principle of its secret ingredients was colchicum [398]. However, it was recommended for many conditions beyond gout and hence it was banned. Later, public clamor brought it back. It was reintroduced into England in 1808, and shortly afterward Dr. James Want discovered its active ingredient to be colchicum.

Having survived the Middle Ages, it seems reasonable to believe that gout continued to be handed down from parent to child as any heritable disease, but specific names of

the affected did not reappear in numbers until the Renaissance. Erasmus noted the relationship between gravel and gout from personal experience. Hertzog Christoph von Wurttenberg, a sufferer from severe gout, wrote a treatise on the subject in 1537 and gave instructions to Martin Luther, a fellow sufferer. Petrarch, in his *Phisicke against Fortune*, wrote much about gout, considering the disease an affliction brought on by God [60]. The Medici have been identified by many observers as endowed with intellectual capacity and gout. Cosimo de' Medici in the 15th Century received gout from his father, Giovanni di Bicci de' Medici. Cosimo suffered greatly and grew old early, leaving the affairs of state to others, but he was highly regarded in his realm. The title, "Father of his People," was conferred upon him posthumously. One of his sons, Piero il Gottoso (Peter the Gouty), who succeeded him at the age of 48 as the ruler of Florence, died only a few years after entering office, and in turn passed on his authority to Lorenzo the Magnificent, grandson of Cosimo, the most outstanding of all the Medici. Lorenzo was patron of the arts and sponsored Michelangelo, another sufferer from the disease [182].

The famous French Renaissance physician, Jean Fernel (1497-1558), and Jerome Cardan (1501-1576) [621] a learned and fashionable physician of Pavia whose consulting practice extended as far as Britain, independently revived the long-forgotten Hippocratic belief that rheumatic fever was an entity separate from podagra. Cardan was the first to point out the predominantly pediatric association of rheumatic fever, when he wrote [212]: "The Morbus Articularis and the podagra are not the same. I have seen many children suffering with arthritis, but never with podagra; and I cannot recollect ever having justly read of one." He observed also that relapses of rheumatic arthritis, unlike those of podagra, tended to occur only in the presence of a fever. This important distinction was reemphasized by the posthumous publication of Baillou's *Liber de Rhumatismo* (1642), but was not completely accepted by the profession until Sydenham (1683) further elucidated the distinction, dividing gout, of which he had a long, personal experience, into the acute and chronic varieties, and describing rheumatic fever with accuracy.

The Holy Roman Emperor Charles V (1500-1558) had his first attack of gout at the age of 28, and was severely handicapped for most of the latter half of his life. He struggled against great odds to rule a great kingdom, meanwhile unable to control a gluttonous appetite nor find any remedy for relief of the gout. He left his throne in 1556 and left this world not long after, a miserable man, "sicke and frustrated of the goute before the High Alter of his chapel in the Escorial" [182].

The Tudor dynasty did not escape the ravages of the scourge [143]. Henry VII, the first of the Tudor Kings, whose marriage to Princess Elizabeth was postponed because of his Majesty's gout, was afflicted, while Phillip II of Spain (son of Charles V), who married Mary Tudor, Queen of England, bowed to the disease six years after he ascended to the throne of the Spanish Empire. By the age of 65 he was bedridden, unable to dress or feed himself, and the victim of unscrupulous surgeons.

William Cecil, the first Baron Burghley (1570-1598), Lord Treasurer of England, became a heavy wine drinker while studying at Cambridge; this may have contributed to his gout but not to his rise to become one of the most powerful men in Europe under Queen Elizabeth I. It was believed that he did more than anyone in his time, not of the nobility, to shape the destiny of England. His intense suffering was widely known, and the number of remedies offered him for relief were many. He bequeathed