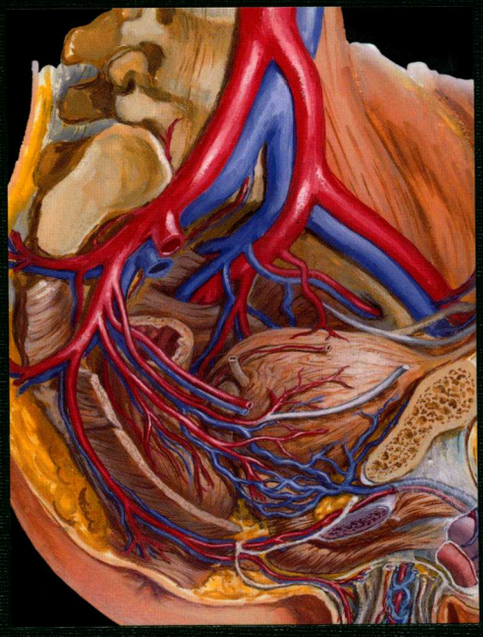
F. Netter M.D.

THE NETTER COLLECTION of Medical Illustrations

2nd Edition

VOLUME 1



Reproductive System

ROGER P. SMITH
PAUL J. TUREK

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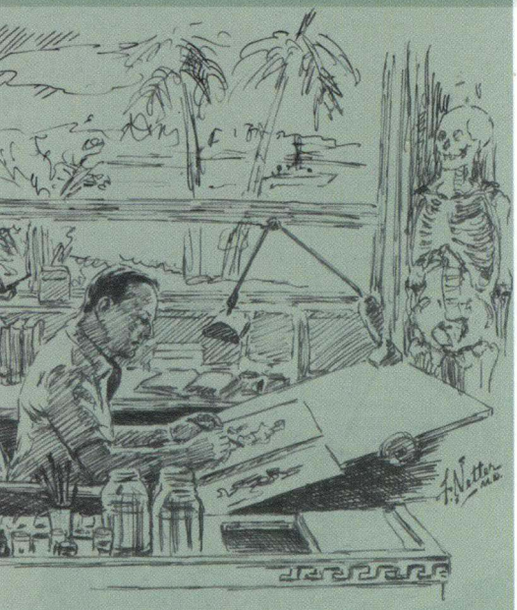
VOLUME 1



The Netter Collection
OF MEDICAL ILLUSTRATIONS
Reproductive System

Second Edition

Roger P. Smith, MD
Robert Munsick Professor of Clinical Obstetrics and Gynecology
Director, Medical Student Education
Director, Division of General Obstetrics and Gynecology
Indiana University School of Medicine
Indianapolis, Indiana

Paul J. Turek, MD
Director, The Turek Clinic
Former Professor and Endowed Chair
University of California, San Francisco
San Francisco, California

Illustrations by
Frank H. Netter, MD, and Carlos A.G. Machado, MD

CONTRIBUTING ILLUSTRATORS
John A. Craig, MD
James A. Perkins, MS, MFA
Kristen Wienandt Marzejon, MS, MFA
Tiffany S. DaVanzo, MA, CMI

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SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103—2899

THE NETTER COLLECTION OF MEDICAL ILLUSTRATIONS: REPRODUCTIVE SYSTEM, Volume 1, Second Edition

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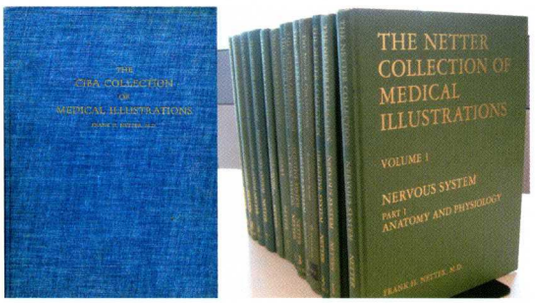
Self-portrait: Dr. Frank Netter at work



The single-volume "blue book" that paved the way for the multivolume *Netter Collection of Medical Illustrations* series, affectionately known as the "green books."

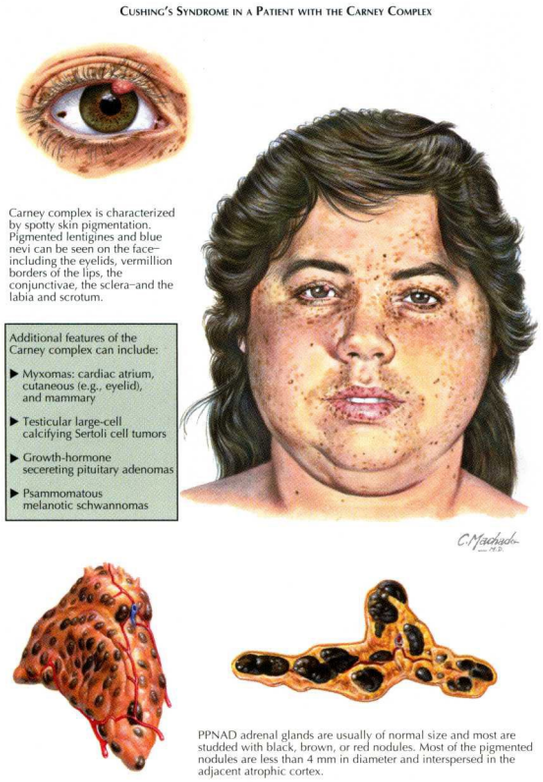
Dr. Frank H. Netter exemplified the distinct vocations of doctor, artist, and teacher. Even more important, he unified them. Netter's illustrations always began with meticulous research into the forms of the body, a philosophy that steered his broad and deep medical understanding. He often said, "Clarification is the goal. No matter how beautifully it is painted, a medical illustration has little value if it does not make clear a medical point." His greatest challenge—and greatest success—was chartering a middle course between artistic clarity and instructional complexity. That success is captured in this series, beginning in 1948, when the first comprehensive collection of Netter's work, a single volume, was published by CIBA Pharmaceuticals. It met with such success that over the following 40 years the collection was expanded into an eight-volume series—each devoted to a single body system.

In this second edition of the legendary series, we are delighted to offer Netter's timeless work, now arranged and informed by modern text and radiologic imaging contributed by field-leading doctors and teachers from world-renowned medical institutions and supplemented with new illustrations created by artists working in the Netter tradition. Inside the classic green covers, students and practitioners will find hundreds of original works of art—the human body in pictures—paired with the latest in expert medical knowledge and innovation, and anchored in the sublime style of Frank Netter.

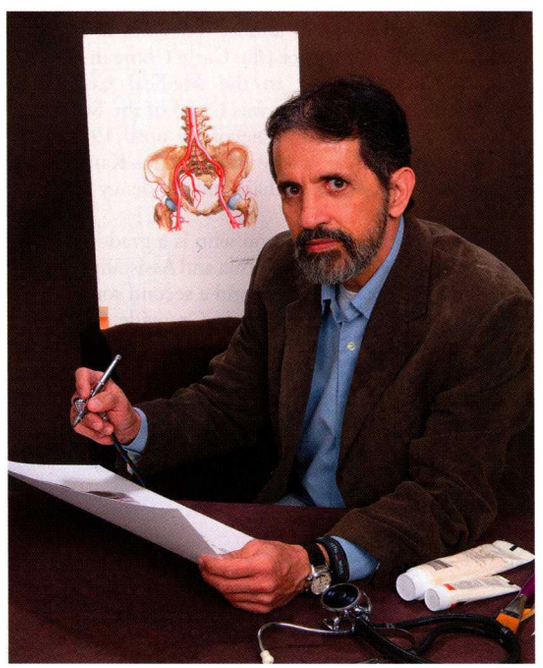
Dr. Carlos Machado was chosen by Novartis to be Dr. Netter's successor. He continues to be the primary artist contributing to the Netter family of products. Dr. Machado says, "For 16 years, in my updating of the illustrations in the *Netter Atlas of Human Anatomy*, as well as many other Netter publications, I have faced the challenging mission of continuing Dr. Netter's legacy, of following and understanding his concepts, and of reproducing his style by using his favorite techniques."

Although the science and teaching of medicine endures changes in terminology, practice, and discovery, some things remain the same. A patient is a patient. A teacher is a teacher. And the pictures of Dr. Netter—he called them pictures, never paintings—remain the same blend of beautiful and instructional resources that have guided physicians' hands and nurtured their imaginations for over half a century.

The original series could not exist without the dedication of all those who edited, authored, or in other ways contributed, nor, of course, without the excellence of Dr. Netter, who is fondly remembered by all who knew him. For this exciting second edition, we also owe our gratitude to the authors, editors, advisors, and artists whose relentless efforts were instrumental in adapting these timeless works into reliable references for today's clinicians in training and in practice. From all of us at Elsevier, we thank you.

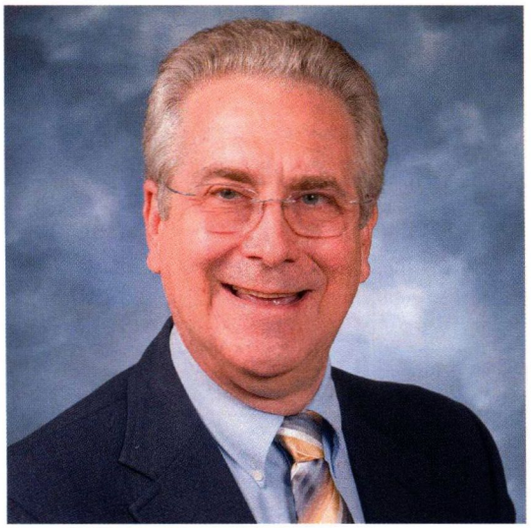


A brand new illustrated plate painted by Carlos Machado, MD, for *The Endocrine System*, Volume 2, ed. 2



Dr. Carlos Machado at work

ABOUT THE EDITORS



Roger P. Smith, MD, is the Robert Munsick Professor of Clinical Obstetrics and Gynecology, Director, Medical Student Education, and Director, Division of General Obstetrics and Gynecology at the Indiana University School of Medicine. Although he has a "CV" that is appropriately long with 90 peer-reviewed papers and 80 books and chapters, he sees himself as a clinician. Dr. Smith received his undergraduate education at Purdue University, and his medical education, internship (in General Surgery), and residency (Ob/Gyn) at Northwestern University in Chicago. He then spent almost ten years in a multidisciplinary group practice (the Carle Clinic in Urbana, Illinois) before moving to the Medical College of Georgia in 1985, where he was Chief of the Section of General Obstetrics and Gynecology until 1999 when he moved to the University of Missouri–Kansas City, where he served as Vice Chair and residency Program Director.

He is married, with one son who is a graduate of the University of Southern California and Assistant Director of Student Publications there and a second son who is a graduate of Denison University in Granville, Ohio, who teaches history to high school students in Fayetteville, North Carolina. Dr. Smith is a collector of antique gumball machines and a semi-professional magician as well.

Paul J. Turek, MD, FACS, FRSM, is Director of The Turek Clinic, an innovative men's health practice in San Francisco. Before retiring from the University of California San Francisco (UCSF) in 2008, he held the Academy of Medical Educators Endowed Chair in Urology Education and was Professor of Urology, Obstetrics, Gynecology and Reproductive Sciences. While at UCSF, he directed the highly competitive Andrology Fellowship Program, directed the Medical Student Clerkship, authored the National Medical Student Curriculum in Urology and founded PROGENI, the Program in the Genetics of Infertility. Dr. Turek attended Yale College, followed by Stanford University Medical School, graduating in 1987. Following his urology residency at the University of Pennsylvania, Dr. Turek undertook fellowship training at Baylor College of Medicine in reproductive microsurgery. He has authored over 200 publications in genetic infertility, the stem cell basis for cancer and spermatogenesis, and men's health epidemiology. In addition, he has also published on several innovative and now popular surgical techniques in male reproductive medicine and is a noted microsurgeon. He is an active member of the American Urological Association and the American Society of Andrology, and is a Fellow of the American College of Surgeons, the Royal College of Physicians (UK), and the Société Internationale d'Urologie. His hobbies include longboard surfing and vintage cars. He lives in the San Francisco Bay Area with his wife and two daughters.

PREFACE

"The challenge, therefore, was to absorb and assimilate the new learning and to exhibit it in a form easily understandable, attractive and so instructive that the essential points could be readily visualized and the more important details grasped without need for search in specific or original publications."

Frank H. Netter MD,
Introduction, *The Netter Collection of Illustrations, Reproductive System*, 1954

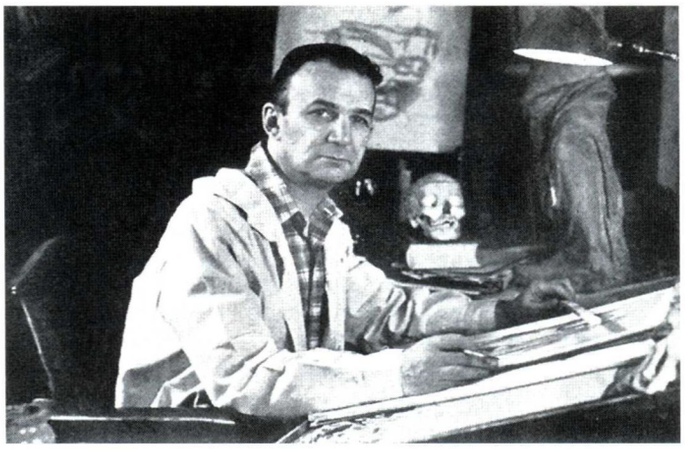
No student of medicine, past or present, is unaware of the extraordinary series of medical illustrations created by Dr. Frank Netter, the master artist-surgeon. This incredible body of work has since been carried forward after Dr. Netter's passing by the talented Carlos Machado, MD, and others, all remarkably gifted medical illustrators. Physicians old and young have looked at these images time and again for the last five decades, returning to them as comfortable sources of clear and clinically succinct information. For many of us, it was this volume that was bought for us by our parents as our first textbook in medical school, and is still cherished to this day.

The Netter series of illustrations underwent 19 printings over 56 years but has never undergone a substantive revision until now. The privilege of editing this monumental tome has been both daunting and revealing. Dr. Netter's art is utterly timeless, highly exact and informed to the point of being prescient. How do you improve on a masterpiece? On the other hand, medicine has change dramatically over the past five decades since this volume first appeared and demands that entirely new and previously unimagined medical knowledge be brought to the readership. Similar to restoring a da Vinci painting or translating a Nabokov novel, editing this volume has highlighted for us both the magnitude of change in medicine and the timelessness of Dr. Netter's art. Consistent with Dr. Netter's philosophy, we have chosen to let the art do most of the speaking and have limited the text to providing context, clarification, and clinical application.

It is our hope that this work will be as treasured and as valued as the original, even if it remains clinically relevant for only a fraction of the time. Join us as we celebrate the beauty, logic, mystery, complexity, and artistic richness of clinical medicine illustrated in this the second edition of the Netter Collection.

Roger P. Smith, MD
Kansas City, Missouri
Paul J. Turek, MD
San Francisco
November 2010

ABOUT THE ARTIST FROM THE FIRST EDITION



For over 12 years it has been my privilege to be what may be called a "regular" in the preparation of the nearly six hundred pictures which, under CIBA's sponsorship, Dr. Netter has painted for the medical profession. As a member of a group proposing the program, as a bystander in the numerous conferences with our consultants, as a reviewer of the sketches and finished paintings and, finally, as editor of this volume, my contacts with Frank Netter have been so frequent and so manifold that I feel qualified to say here a few words about the man and about his methods.

Netter's expressional power with brush and color, his craftsmanship, needs no further comment. The pictures themselves are, in this respect, the most eloquent witnesses. What the pictures, however, do not reflect to the mere spectator is the amount of work and study expended before the artist starts the process of transmitting onto paper his ideas about an anatomic or pathologic problem or his concepts of the multitudinous facts and details. The simplicity and unsophisticated portrayal of the subject matter make it seem that these plates have come into existence with miraculous ease but, in reality, nothing but the artist's formative act of painting is spontaneous.

Never satisfied with the mere reporting of facts or with an unimaginative copying of nature, as can be done with pencil and camera alike, Netter's creative forces are generated only after a complete, intellectual assimilation of a subject, its scientific background and its theoretical, as well as practical, significance. Rarely does he permit himself a short cut, because he incessantly questions the correctness of his own memory. He starts all over again. Whether essential or bordering on the trivial, all anatomic details are recapitulated. All available texts and other publications, particularly the pertinent literature of the past 25 years, are read, checked, rechecked, and compared. It is actually like classwork, with the main difference that our "student" performs his task with the support of an enormously widened horizon and boundless experience, especially with regard to the relationship of form and function.

Though, as disclosed in the sessions with the consultants, a certain degree of scientific curiosity guides this prying into the original sources, the mainspring is his irresistible compulsion to penetrate and to comprehend as a physician before liberating the creative forces of the artist. In this way Netter's final achievements cause the sensation of a well-rounded concept and a vivid reproduction in contrast to an inanimate representation of endless details. Some of the pictures, of course, demand less thought and absorption of knowledge than do others. This, however, is of minor influence on the total energy expended on the scholarly approach, because, at least in a collection of pictures such as those in this book, Netter endeavors to dramatize a complete narrative of an organ and its structural relationship to normal, as well as disturbed, function. The single entities, *e.g.*, of a specific disease, become a part of the whole story rather than a detached object.

Netter's concentration during such a "study period" is so intense that it works like a lock for other brain activities—a sometimes rather painful discovery for those surrounding him, as well as for an editor. It is rather difficult to approach him or to get action in any affair other than the one occupying his mind. But once Netter has mastered all the intricacies of the project-in-the-making, he is immediately available for the next one, into which he plunges, then, without pause. The "appropriation process" for a new topic starts, usually, in the first conference with the chosen consultant. There, the primary outline of a chapter is made, and the number and order of pictures are anticipated, though the ultimate number and order are never the same as originally conceived. Specimens and countless slides are examined. Netter, on these occasions, mostly looks on and listens. Rarely is he observed to make a written note during these consultations and, if he puts something on paper, it is usually a rough sketch. This technique is used also in his reading. Where others make excerpts and abstracts, Frank Netter uses the pencil to draw a few lines.

While the zealous submersion in books and articles goes on, subsequent meetings with the consultants follow at intervals of a month or two. But the character of these meetings changes markedly after the first conference. Usually during the second session, when Netter arrives with a pack of sketches, his acquired familiarity with the field of the expert asserts itself. Mutual trust and respect between the consultant and Netter develop with remarkable speed. The sincere and friendly relations, without which I do not think Frank Netter could work, are attributable, in part, to his professional knowledge and to the acuteness of his mind but, essentially, to his human personality, his amiability and his sound sense of humor.

During the years of indecision—long past—when he did not know whether to turn to a medical career or follow his inborn talents as a painter, Netter succeeded in amalgamating physician and artist. With a genuine seriousness and readiness to accept the responsibility connotive of a physician and the impelling urge of an artist, he has now surrendered to his life's task—to depict the human body and the causes and processes of its ailments in a forcefully instructive, easily comprehensible, unconventional and artistic form.

E. Oppenheimer, M.D.

INTRODUCTION TO THE FIRST EDITION

An attempt to determine the natal hours of modern scientific anatomy is as unavailing as would be an effort to set an exact date for the beginning of the Renaissance era. The changes of mind, intellect and interest, of conceptual thinking, which we in our time admire in retrospect, began slowly and developed only over a span of two centuries. One can, however, scarcely go wrong in stating that the momentum for scientific research was at no time (except perhaps our own) as poignant as in the fifteenth and sixteenth centuries. This was the period in which philosophers, scientists, physicians and the great artists alike became not only interested in but devoted to the study of forms and structures inside the human body. The motives of an Andrea del Verrocchio (1435–1488), of a Donatello (1386–1466), of a Leonardo da Vinci (1452–1519), of a Michelangelo Buonarroti (1475–1564), of a Raffaello Santi (1483–1520)—just to name a few of the best-known Renaissance artists—for drawing anatomic subjects are difficult to explain. Whether it was sheer curiosity, a fashionable trend, scientific interest or other reasons that prompted them to leave to posterity these magnificent works of art concerned with the muscles, bones and internal parts of Homo sapiens, one can be sure that these drawings were not meant to accompany or to clarify the anatomist's dissections and descriptions. Nevertheless, the painters of that period can be designated as the creators of medical illustration, because it may safely be assumed that the first useful instrument that provided a general and more popular knowledge of the inner structures of the human body was not the knife of the dissecting anatomist or his description written in Latin, but the pencil of the artist. Health, standing second only to nutrition in the minds of people of all times, must have been a "hot news" topic half a millennium ago as it is in our day, in which the so-called "science writer" has taken over the function of making accessible to contemporary intellectuals what the language or idiom of the scientist has left inaccessible.

With the exception of Leonardo, whose geniality and universal inquisitiveness in every field of science led him to be far ahead of his contemporaries, none of the many excellent artists who took a fancy to drawing or painting anatomic subject matter contributed to the factual knowledge of anatomy or medicine, but it became a landmark of extraordinary significance when Andreas Vesalius (1514–1564) wrote his *De Corporis Humani Fabrica* and found in John de Calcar (1499–1546), Flemish painter and pupil of Titian (1477–1576), the congenial artist who supplemented the great anatomist's revolutionizing work with his magnificent illustrations, the first true-to-life reproductions of the structures of the human organism. The "Magna Carta" of anatomy, as posterity has called Vesalius' opus, was engendered by an ideal union of scientist and artist as two equal partners, as far as creative power, each in his own field, goes.

The mystery of the propagation of life occupied the minds and emotions of mankind from the time the deities of fertility demanded devotion and sacrifice. One naturally is inclined, therefore, to expect that in ages progressive in science, such as the Renaissance, the knowledge of the generative tract, or more generally, the search to elucidate procreative processes, would be exposed to special benefit and encouragement. This, however, seems not to be the case, perhaps because specialization was a thing of naught to Renaissance mentality. The advances in knowledge of the anatomy of the reproductive system during the time of Vesalius and the 300 years after him were as respectable as those in the lore of all other sciences, but not more so. Remarkable contributions and disclosures were reported, as witnessed by the many anatomic designations which still carry the names of their discoverers, such as Gabriello Fallopio (1523–1562), Thomas Wharton (1614–1673), Regnier de Graaf (1641–1673), Anton Nuck (1650–1692), Edward Tyson (1650–1708), Caspar Bartholin (1655–1738), Alexis Littré (1658–1726), William Cowper (1666–1709), James Douglas (1675–1742), Kaspar Friedrich Wolff (1733–1794), Johannes Müller (1801–1852) and others, names that will be encountered on many pages of this book. But anatomy of the genital organs and the physiology (or pathology) of reproduction were not favored by the appearance of a Harvey who revolutionized the physiology of circulation and, with it, of medicine in general.

It is from this historical aspect the more surprising to observe that under our own eyes, as a matter of fact within scarcely more than a single generation, so many new phenomena have come to light, and discoveries so revolutionizing have been made that our concepts and knowledge of the physiology and pathology of reproduction have undergone fundamental changes. Endocrinologic research has presented to us the story of the mutual relationship between the pituitary gland and the gonads and of the activities and functions of the secretion products of these organs on the genitals and other parts of the body. The impact of these scientific accomplishments on the practice of medicine, particularly for the interpretation of genito-urinary and gynecologic diseases, has been tremendous. In addition to the progress in endocrinology, we have lived to see simultaneously the rise of chemotherapy, which inaugurated a magic alteration in the character, management and prognosis of the formerly most frequent diseases of the reproductive structures.

This progress is not, of course, as everybody knows, the result of the genius of one or of a few single individuals; it is the yield of the efforts of an endless number of scientists from all parts of the world and—in view of the foregoing paragraphs—it should also be remembered that the speed and the intensity with which this progress has been achieved have not been restricted solitarily to the science of reproductive physiology or pathology of the genital organs but belong to the scientific tide of our times, as can be noticed in all branches of science.

These chips of thoughts have been uttered here, because those about the early artist-illustrators occupied my mind in the few hours of leisure permitted me during the preparation of this book, and those about the recent changes in our specific topic suggested themselves continuously during the preparation of the new and the checking of the older plates. The situation the advancements in our knowledge have caused, as indicated sketchily in the foregoing, presented a specific task and, concurrently, a straightforward challenge. In spite of my intentions and efforts, shared, I am sure, by all responsible practicing physicians, to "keep informed", many of the facts, facets, connections, concepts, etc., which experimental biology and medicine have brought to light, were novelties to me, as they must be or have been to a generation of still-active physicians—those who studied medicine during the time of my school days or even before. The challenge, therefore, was to absorb and assimilate the new learning and to exhibit it in a form easily understandable, attractive and so instructive that the essential points could be readily visualized and the more important details grasped without need for search in specific or original publications.

The subjects of the pictures were selected on the basis of what seemed to be of the greatest clinical import and interest. Although we aimed to secure a reasonably complete coverage, it is obvious that not everything could be included. With the newer knowledge crowding in so rapidly upon the old and from so many sources—chemistry, biology, anatomy, physiology, pathology, etc .—with the accumulation of so many pertinent data, the book could have grown to twice its size. Would we, with greater completeness, have better served the student or busy practitioner with his difficulties in following and correlating? It was the opinion of all concerned that this would not have been the case and that the adopted restriction would prove more helpful. Actually, the book grew much larger than was originally anticipated, particularly because it was felt that certain "correlation" or "summation" plates, *e.g.*, pages 5, 105, 115, 120, 162, 175, 211, 213, 214, and 241, were necessary for the mission we flattered ourselves this book could fulfill.

In view of the steadily increasing number of plates, it was natural that at some time during the preparation of the book the question should be seriously discussed and considered whether the treatise on the male and female reproductive systems should appear as separately bound books or in one volume under the same cover. The decision fell in favour of a single volume containing the exhibit of both genital tracts, because separation into two volumes would have seriously counteracted my earnest striving for integration of the knowledge on the two tracts. It was also felt very strongly that the small monetary advantage that would have been gained by those distinctly interested in only one part of the book—in all probability a small minority—would be more than compensated by the educational benefit conferred by the contiguity of the topics and the amalgamation of the two parts.

Whereas in the series of illustrations published in earlier years, the gross anatomy of an organ was reviewed in direct association with the pictures on the pathology of that organ, it will be found that for the purpose of this book the anatomy of the organs follows the description of the anatomy of the whole system. In other words, Section II and Section VI contain, respectively, the accounts of the male and the female genital tracts in toto, succeeded by more detailed depictions of the parts. This arrangement was thought to be more expedient from the didactic and more logical from the organizational points of view. As a consequence of this method, it will be noted that Section VI, in contrast to the other sections, each of which was compiled and prepared with one consultant, lists numerous collaborators, each describing the anatomy of that part of the tract for which he was consultant in the sections on the diseases. The danger of inconsistencies or lack of uniformity in one section that might have been incidental to this concurrent effort of a plurality was happily circumvented by the splendid adaptability of each individual coauthor. Duplication of features within the paintings were avoided by appropriate planning. Repetitions, occurring when the essays were submitted, could be eliminated

without any difficulty, although a few were allowed to remain intentionally, mostly because it seemed warranted to discuss certain points from different aspects.

In Section VI we have also inserted pictures not originally painted for the series collected in this book. Neuropathways of Parturition (page 105) seemed, however, to fit in with the illustrations of the innervation of the female genital tract and to make a desirable supplement. I am greatly obliged to *Dr. Hingson* for his approval of the use of this picture together with his rearranged explanatory text.

From *Dr. Decker's* article in CIBA CLINICAL SYMPOSIA (4:201 (August-September) 1952), we took one plate demonstrating the technique of Culdoscopy (page 123) and, in abbreviated form, his description. The culdoscopic views used in Sections X and XII are from the same source. I drew them from actual observations through the culdoscope in Dr. Decker's clinic. His co-operative courtesy and permission are gratefully acknowledged.

The plates on diagnostic topics, I would like to emphasize, are by no means intended as instructions for the execution of such procedures, nor are they or the concomitant texts proposed as precepts for the evaluation of the results. It would not have been difficult to add more diagnostic features and to describe with brush and pen a great many technical details and also a great many varieties of diagnostic results. This was considered definitely beyond the scope and purpose of this book. The same holds true for the illustrating of operative procedures. The four plates pictorializing the Surgical Approaches to the prostate (pages 58–61) were included because Dr. Vest and I were convinced they would satisfy a need of the nonurologists and would acquaint them with the urological reasonings underlying the urologist's proposals for the management of the recommended patient. No such necessity seemed to exist for the great variety of surgical techniques in the field of gynecology. It is great fun for an artist to paint surgical procedures in their various phases, particularly when properly directed by an experienced surgeon. I did not surrender to such temptation, because it would have jeopardized the adopted principal purpose of the book, which, in short, is to promote the understanding of medical facts and problems but not to show how things are done. For the same reason we omitted from this volume topics concerned with obstetrics, in spite of the fact that pictures of this kind were available, as I had made some for CIBA in whose CLINICAL SYMPOSIA (4:215 (October) 1952) they appeared.

Several pictures dealing with the development of the reproductive systems or organs were added, because of the fact that the interpretation and understanding of most congenital anomalies and also of some pathologic conditions are difficult, if at all possible, without at least a cursory idea of the embryology of the generative organs. A brief, admittedly oversimplified survey of the formation of the fetal internal and external genitalia, therefore, seemed in order (pages 2 and 3). With these plates, as with those demonstrating in rudimentary fashion the development and implantation of the ovum and fetal membranes (pages 217 and 218), nothing was further from my mind than to introduce the reader into the complex details that embryologic research has brought to light. The scientific importance of these details is beyond question, but they have—at least to my knowledge and at this moment—no direct bearing on the interest of the majority of those for whom this book has been prepared.

To mention all the deliberations and reflections which, in the course of several years, shaped this book is impossible, but I would like to say a few words more to express my appreciation to each of the consultants. I agree wholeheartedly with the editor's statement in the preface that this volume in its present form could not have been executed without their unerring and intense devotion. The support I received from their knowledge and experience and from the material they placed at my disposal was vitally essential for the entire project.

Dr. Vest, who patronized Sections I through V and Section XIV, is one of my steadfast, unwavering collaborators and has become a long-tried, but still critical, friend. For over a decade I have been fortunate enough to enjoy not only his giving freely of his expert information but also his remarkable comprehension of what is didactically important and unimportant. I deeply regret that with the completion of this series of illustrations I will have to forego his co-operation for the present, and I await anxiously that time which will enable me again to have him participate in my efforts, when we are ready for the illustrations of the urinary tract.

For the plates covering the complex topic, Testicular Failure (pages 73–79), in Dr. Vest's Section V, we received stimulus and help from *Dr. Warren O. Nelson* (University of Iowa), who not only offered his proficient advice derived from his long-time special study of the anatomy, physiology and pathology of the human testis, but provided us also with a great number of slides from his impressive collection. From this source stem also the microscopic views on pages 73 and 82.

The treatment of the subject matter on Testicular Failure presented a delicate problem, because no final concept of the various conditions has been agreed upon. The knowledge in this field is still in an evolutionary state, but by the importance these conditions assume nowadays in the practice of medicine, we were forced, so to say, to take a stand and to compromise with the general principle maintained in this book, namely, to avoid controversial matters. It is realized that the concept we submit in the presentation of Testicular Failure might not find approval with all investigators, and the reader should understand that in due course new findings may be recorded which may substantially change the information now available.

In connection with Dr. Vest's sections, I would like, furthermore, to thank *Dr. J. E. Kindred* (University of Virginia) for his generosity in permitting me to make free use of his own drawing of the phases of spermatogenesis, which I followed in great detail, in preparing the schematic picture on page 25.

A sizeable part of the book—altogether 44 plates—were under the consultative sponsorship of *Dr. Gaines*, whose active interest in my work also dates back over a decennium. His participation in this book began with his contribution to Section VI, continued with Section VII and ended with his collaborative effort and preparation of the learned text for Section XI. Diseases of the Ovary represents surely, with regard to organizational arrangement and factual information, one of the most complicated chapters of morbid anatomy and histopathology. Dr. Gaines' decisive counseling in the selection of the conditions to be portrayed and his support of my aim to demonstrate exemplary rather than specific entities were of indispensable help, which I would like to recognize with my profound thanks. A certain restraint was necessary, naturally, in all sections but in none more essential than in Section XI, where a limitless possibility to demonstrate more and more specimens of cysts or tumors can readily be envisaged.

The series on Major Anatomy and Pathology of the Breast, prepared and issued in 1946, has been in such demand since its appearance that it seemed advisable to insert Section XIII in this volume, dealing with the entire reproductive system. *Dr. Geschickter*, to whom I was indebted for his counsel when the pictures were made, gladly agreed to check the plates and to revise the texts. Except for the substitution of one microscopic view and omission of one plate, the series of paintings remained unchanged and was found to meet modern requirements. Dr. Geschickter's attending to overhauling the texts—a rather troublesome task—is deeply appreciated.

For the composition of the chapter on Diseases of the Uterus (Section IX) and the cyclic function of this organ (part of Section VI), it was my great fortune to have the collaboration of *Dr. Sturgis*. I will never forget the stimulus and benefit I received from his critical attitude on one side and his enthusiasm for the whole book on the other. It was sheer pleasure to work with him. Similarly, as with the plates on Testicular Failure, the treatment of the physiology of menstruation was not easy, because too many unknowns still obscure the prospect of a clear-cut, invulnerable concept. My admiration for Dr. Sturgis' instructive contribution and for the way he mastered the difficulties are only surpassed by my gratitude to the fate that brought us together.

My reverence for *Dr. Rubin* goes back to my school days, and it made me very happy that I could obtain his and *Dr. Novak's* co-operation for the production of Section X. The major task and the tiresome working out of the details fell upon the shoulders of Dr. Novak, whose sound conservatism and astute wisdom provided the book and me with a vivid enlightenment. I am under special obligation to Dr. Novak for his handling of matter and text, because, more than in other sections, we felt, while preparing the chapter on Diseases of the Fallopian Tubes, that the sectional arrangement according to organs had introduced some shortcomings. The congenital anomalies, and particularly the infections, could have been described in a more logical fashion in a discourse of these conditions affecting the entire female tract. Since division according to organ pathology was due to the chronologic development of the book and its parts, and since a change would have caused a number of other handicaps, a compromise became necessary, which, thanks to the discernment of the collaborators, was not too difficult.

Dr. Assali and *Dr. Zeek* have made the much-neglected pathology of the placenta and concurrent clinical phenomena their life's task. It was a thrilling experience for me to meet them, and I am deeply indebted to these two scientists for the interest they displayed and for the many hours they spent in acquainting me with the results of their own studies and the status of our knowledge in this sphere of science.

Last, because it concerns the most recent pictures I painted for this volume but assuredly not least, my thanks are tendered to *Dr. Mitchell* for his intelligent guidance in our selection of the conditions presented in Section VIII. His competent judgment was, furthermore, of great help in filling certain gaps in Section VI which had to be closed in order to make this section what I wanted it to be—an exhaustive survey of the anatomy of the female genital tract. Dr. Mitchell's illuminating texts which accompany my pictures in these two sections speak for themselves.

Finally, I must try to express my appreciation for the wonderful co-operation and encouragement I received from *Dr. Oppenheimer*. Officially, he was the editor of this volume, but actually he was far more—a friend, a counselor, a collaborator and a ceaseless co-worker. His broad knowledge, his progressive point of view, his flexible attitude helped tremendously in solving the most difficult problems.

Frank H. Netter, M.D.

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CONTENTS

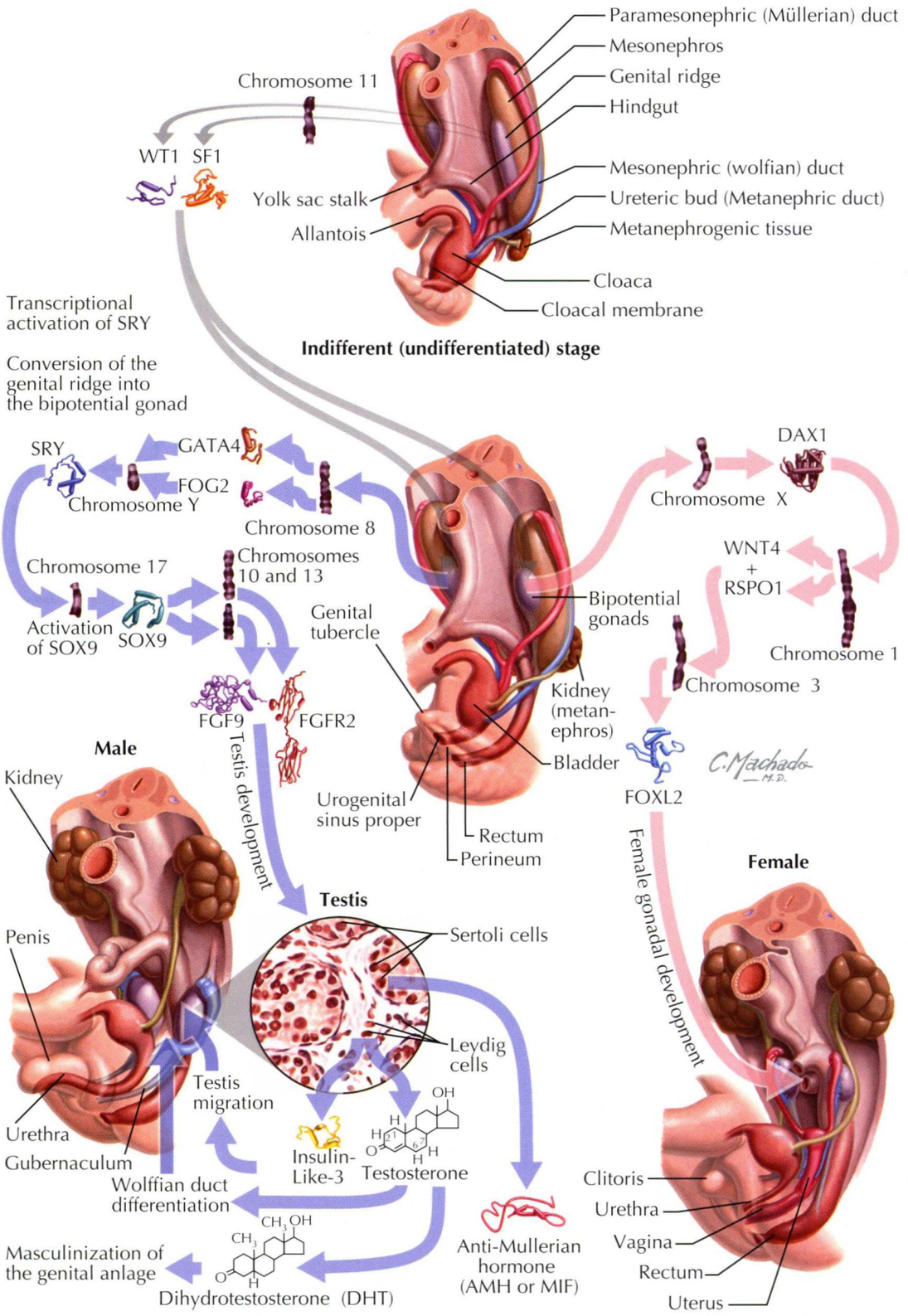
DEVELOPMENT OF THE GENITAL TRACTS AND FUNCTIONAL RELATIONSHIPS OF THE GONADS

Genetics and Biology of Early Reproductive Tract Development

Most living species have some form of sex-determination system that drives the development and expression of sexual characteristics in that organism. Sex determination can be genetic or can be a consequence of environmental or social variables. In humans, sex determination is genetic and is governed by specific genes and chromosomes. It is believed that the two human sex chromosomes (X and Y) evolved from other nonsex chromosomes (autosomes) 300 million years ago. Human females have two of the same kind of sex chromosome (XX), whereas males have two distinct sex chromosomes (XY). However, both male and female features can rarely be found in one individual, and it is possible to have XY women and XX men. Analysis of such individuals has revealed the genes of sex determination, including SRY (sex-determining region Y gene) on the short arm of the Y chromosome, which is important for maleness. The *SRY* gene product is a protein that harbors a high-mobility group box (HMG) sequence, a highly conserved DNA-binding motif that kinks DNA. This DNA-bending effect alters gene expression, leading to formation of a testis and subsequently to the male phenotype. Notably, XY individuals who lack the *SRY* gene on the Y chromosome are phenotypic females.

It is now clear that the *SRY* gene does not act in isolation to determine human sex. Other genes in other locations are also important for complete male sexual differentiation. DAX1, a nuclear hormone receptor, can alter *SRY* activity during development by suppressing genes downstream to *SRY* that would normally induce testis differentiation. A second gene, *WNT4*, largely confined to the adult ovary, may also serve as an "anti-testis" gene. Indeed, the discovery of these genes has significantly altered theories of sex determination. Previously, *SRY* gene presence was thought to determine male gonadal development from the bipotential gonad. The female genotype was considered the "default" developmental pathway for gonads. It is now clear that genes such as *WNT4* and *DAX1* can proactively induce female gonadal development, even in the presence of *SRY*.

Once gonadal sex is determined, several other events must occur for normal male sexual differentiation. Within the testis, Leydig cells make testosterone, a hormone that is critical for development of the internal genitalia, including the vas deferens, epididymis, and seminal vesicles through wolffian duct differentiation. Leydig cells also synthesize insulin-like-3 to promote transabdominal testis migration that begins testis descent into the scrotum. Dihydrotestosterone (DHT), a testosterone metabolite, masculinizes the genital anlage to form the external genitalia, including the penis and scrotum as well as the prostate. In addition, Sertoli cells within the developing testis synthesize *anti-müllerian hormone (AMH* or *MIF)*, which prevents the müllerian duct from developing into uterus and fallopian tubes and helps the early germ cells remain quiescent in the developing testis. Deficiencies in any of these developmental pathways generally results in either birth defects or intersex disorders. Such development disorders, formerly termed *true* or *pseudohermaphroditism*, can include chromosomal abnormalities, ambiguous genitalia, phenotypic sex anomalies, or true intersex states.



Homologues of the Internal Genitalia

Although sex is determined at the time of fertilization, phenotypic gender is determined by a complex tissue differentiation process that begins in the medial genital thickening or ridges on the posterior surface of the embryonic body cavity. During the 5th fetal week, primordial germ cells migrate from the yolk sac to the posterior body wall and induce the formation of genital ridges on either side of the midline. Here, these migrating cells induce the formation of undifferentiated primitive sex cords.

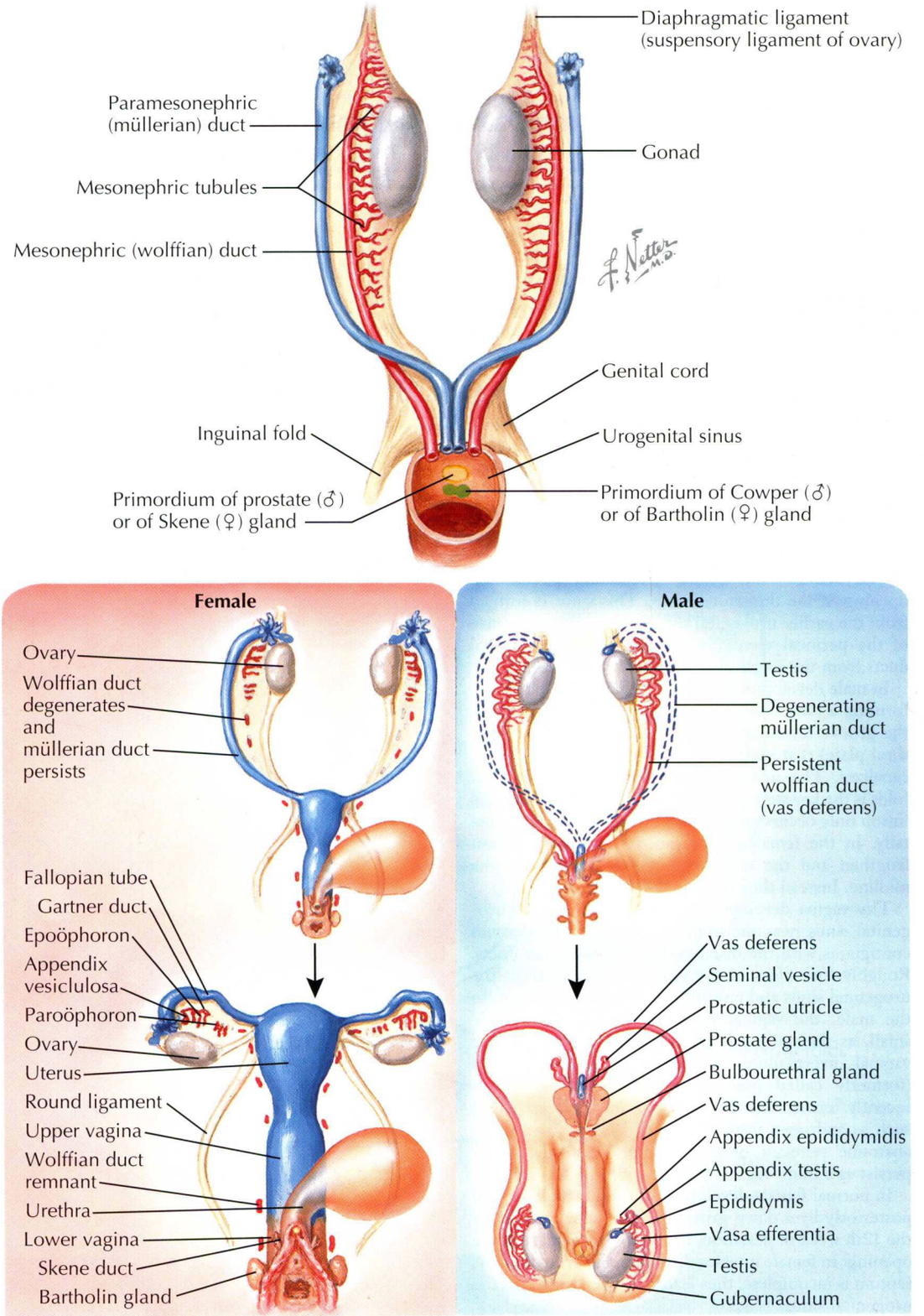
Signaled by the arrival of primordial germ cells, two sets of paired genital ducts, the mesonephric or nephric (wolffian) ducts and the paramesonephric (müllerian) ducts also develop. The mesonephros is a prominent excretory structure that consists of a series of mesonephric tubules that connect with the elongating mesonephric (wolffian) ducts as the latter extend caudally until they terminate in the urogenital sinus on each side of the midline. The paramesonephric ducts develop lateral to each of the mesonephric ducts and are derived from the evagination of the coelomic epithelium. The cephalad ends open directly into the peritoneal cavity, whereas the distal ends grow caudally, fuse in the lower midline, form the uterovaginal primordium, and join the urogenital sinus as an elevation, the müllerian tubercle, which separates the urogenital area from the more posterior gut.

Under the influence of the *SRY* gene in the male primitive sex cord, the mesonephric (wolffian) ducts are maintained during development. As the developing male Sertoli cells begin to differentiate in response to SRY, they secrete a glycoprotein hormone, müllerian-inhibiting substance (MIS) or anti-müllerian hormone (AMH) that causes the paramesonephric (müllerian) ducts to regress rapidly between the 8th and 10th fetal weeks. Müllerian duct remnants in the male include the appendix testis and the prostatic utricle. In females, MIS is not present, so müllerian ducts remain, and the mesonephric tubules and ducts degenerate in the absence of androgens, often resulting in remnant epoöphoron and paroöphoron cystic structures within the ovarian mesentery and Gartner duct cysts within the anterolateral vaginal wall. These structures are clinically important because they may develop into sizable and symptomatic cysts (see Plates 8-13 and 9-13).

In the male, under the influence of testosterone secreted by Leydig cells at 9 to 10 weeks, the majority of the mesonephric ducts develop into the vas deferens and body (corpus) and tail (cauda) of the epididymis. The mesonephric tubules nearest to presumptive testis form the globus major or caput of the epididymis and the efferent ductules that connect to the testis, forming ducts to transport sperm. The more cranial mesonephric tubules develop into the vestigial appendix epididymis, and the more caudal tubules may develop into remnants called paradidymis. The seminal vesicles sprout from the distal ends of the mesonephric ducts, whereas the prostate and bulbourethral glands develop from the urogenital sinus, thus revealing different embryologic origins. In the fully developed male embryo, the distal orifice of the mesonephric duct (ejaculatory duct) terminates in the verumontanum on the floor of the prostatic urethra.

During the 10th week of gestation in females, in the absence of MIS and androgens, the primordial müllerian ducts remain separate and form the fallopian tubes superiorly. At their caudal ends, the ducts join, fuse, and form a common channel called the uterovaginal canal, which later develops into the uterus and proximal four-fifths of the vagina. The remainder of the distal vagina forms from paired thickenings on the posterior urogenital sinus called sinovaginal bulbs and the vaginal plate, whose origin is not clear.

Intersex disorders can result from failure of the müllerian or wolffian ducts to regress completely. An example of this is hernia uteri inguinale or persistent müllerian duct syndrome, in which MIS deficiency or receptor abnormalities cause persistence of müllerian duct structures in an otherwise phenotypically normal male. This is commonly diagnosed during exploration for an infant hernia or undescended testicle because the müllerian structures can tether the testis in the abdomen and restrict normal scrotal descent. Vestigial remnants of the wolffian duct can also exist in fully developed females. Vestiges of the male prostate may appear as periurethral ducts in the female (see Plate 7-5). In addition, homologues of male Cowper glands are the major vestibular glands (Bartholin glands) in the female (see Plate 6-16).



HOMOLOGUES OF EXTERNAL GENITALIA

Before 9 weeks of gestation, both sexes have identical external genitalia, characterized by a urogenital sinus. At this undifferentiated stage, the external genitalia consist of a genital tubercle above a urethral groove. Lateral to this are urethral or urogenital folds and even more lateral are the labioscrotal swellings or folds. The male and female derivatives from these structures are shown.

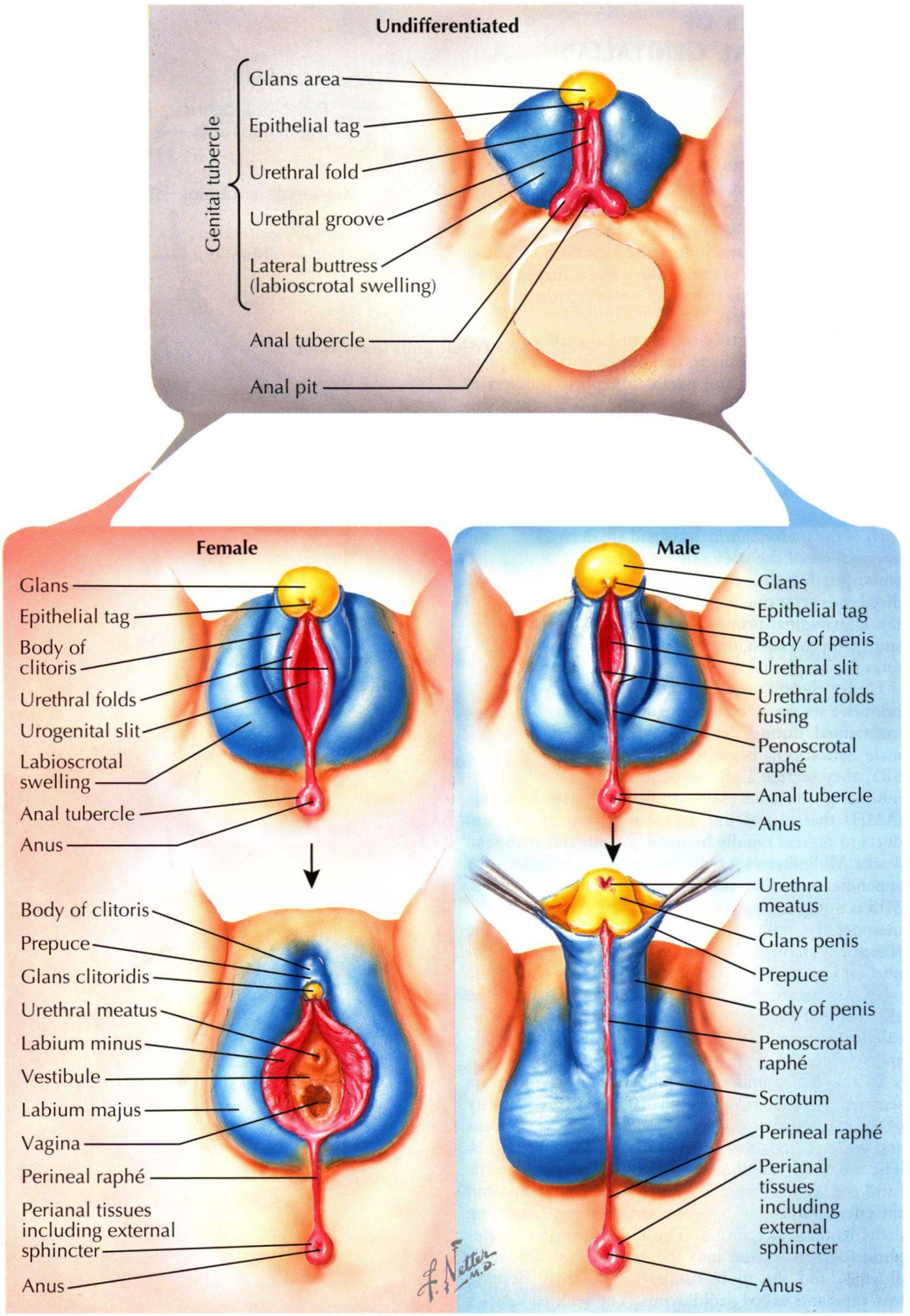
The bladder and genital ducts find a common opening in the urogenital sinus. This sinus is formed from the earlier urogenital slit, which is a consequence of the perineal membrane separating the urogenital ducts from the single cloacal opening.

In male development, the genital tubercle elongates, forming a long urethral groove. The distal portion of the groove terminates in a solid epithelial plate (urethral plate) that extends into the glans penis and later canalizes. The midline fusion of the lateral urethral folds is the key step in forming a penile urethra, but this fusion only occurs after the urethral plate canalizes distally. In the female, the primitive structures do not lengthen and the urethral folds do not fuse in the midline. Instead they become the labia majora.

The vagina develops as a diverticulum of the urogenital sinus near the müllerian tubercle. It becomes contiguous with the distal end of the müllerian ducts. Roughly four-fifths of the vagina originates from the urogenital sinus and one-fifth is of müllerian origin. In the male, the vaginal remnant is usually extremely small, as the müllerian structures atrophy before the vaginal diverticulum develops. In intersex disorders (formerly called pseudohermaphroditism and most recently termed *disorders of sexual development* [DSD]) such as androgen insensitivity syndrome, however, an anatomic remnant of the vaginal diverticulum may persist as a blind vaginal pouch.

In normal female development, the vagina is pushed posteriorly by a down growth of connective tissue. By the 12th week of gestation, it acquires its own, separate opening. In female intersex disorders, the growth of this septum is incomplete, thus leading to persistence of the urogenital sinus.

Male and female external genitalia in the first trimester of development appear remarkably similar. The principal distinctions between them are the location and size of the vaginal diverticulum, the size of the phallus, and the degree of fusion of the urethral folds and the labioscrotal swellings.



FACTORS DETERMINING DIFFERENTIATION OF THE EXTERNAL GENITALIA

Similar to the genital ducts, there is a tendency for the external genitalia to develop along female lines. Masculinization of the genital ducts is induced by androgenic hormones, principally testosterone from Leydig cells in the fetal testis during the differentiation process. More important than the source of androgens, however, is the timing and amount of hormone. Examples of this include inappropriate androgen exposure from congenital adrenal hyperplasia or from the maternal circulation, both of which can induce various degrees of masculinization of the female system characteristic of intersex disorders. By the 12th week, androgenic exposure will no longer cause fusion of the urethral and labioscrotal folds in the female, as the vagina has migrated fully posteriorly. Clitoral hypertrophy, however, may still result from such exposures at any time in fetal life or even after birth.

Testosterone and Estrogen Synthesis

Under the control of the anterior pituitary, three glands produce steroid hormones involved in reproduction: the adrenal cortex responding to adrenocorticotropic hormone (ACTH), and the ovary and testis, both under the influence of the gonadotropin luteinizing hormone (LH). For the majority of sex hormones that result from this stimulation, cholesterol is the precursor molecule.

In each of these organs, side chains are degraded from cholesterol to form pregnenolone and dehydroepiandrosterone (DHEA). In humans, DHEA is the dominant sex steroid and precursor or prohormone to all other steroid sex hormones, including testosterone and estrogens. In the blood, most DHEA is found in its sulfate-bound form, DHEAS, and not in the free form. DHEA supplements are often used as muscle-building or performance-enhancing drugs by athletes. However, randomized placebo-controlled trials have found that DHEA supplementation has no effect on lean body mass, strength, or testosterone levels. Pregnenolone is converted to progesterone, which by degradation of its side chain is converted to androstenedione and then to testosterone. The latter two of these hormones are the main products of testicular Leydig cells. Androstenedione, also termed "andro," is an FDA-banned dietary supplement that is also taken by athletes to improve performance. In the ovary, synthesis of androstenedione by theca interna cells and its subsequent conversion to estrone in follicular granulosa cells, along with conversion of testosterone to estradiol by aromatases, comprise the main secretory products. With polycystic ovary syndrome, enzymatic conversion of testosterone to estradiol in the ovary is impaired and DHEAS levels are elevated, leading to an androgenized phenotype in affected women. Estriol, a product of estrone metabolism in the placenta during pregnancy, is the third major estrogenic hormone in the female but is the least potent biologically.

About 5% of normal daily testosterone product is derived from the adrenal cortex, and the remainder is secreted by the testis into the systemic circulation. In the plasma, testosterone is virtually entirely bound (98%) by proteins such as sex hormone binding globulin or albumin. The remainder of testosterone (2%) exists in a free or unbound form, which is the active fraction. Testosterone is conjugated in the liver and excreted by the kidney in this water-soluble form. Circulating estrogens have a similar bioavailability profile and are also carried on plasma proteins, notably albumin. Inactivation of estrogen occurs in the liver through conversion to less active metabolites (estrone, estriol), by conjugation to glucuronic acid, or by oxidation to inert compounds. There is also considerable enterohepatic circulation of estrogens in the bile. Estrogen, testosterone, and their metabolites are ultimately excreted by the kidney, for the most part in the form of 17-ketosteroids in which a ketone group is present on the steroid ring. Examples of 17-ketosteroids include androstenedione, androsterone, estrone, and DHEA.

Although important for premenopausal women, the value of estrogen and progesterone supplementation in postmenopausal women is controversial. A randomized, controlled trial of 15,730 women in the Women's Health Initiative was stopped early, after 5.6 years, because of the finding that risks (including stroke, blood clots, and breast cancer) outweighed benefits (lower risk of hip fractures and colon cancer) among subjects taking hormone supplements. Similarly, the value of testosterone supplements in older men who have reached andropause (androgen deficiency with age) is even more controversial, as large, randomized, placebo controlled trials of sufficient duration to assess long-term clinical outcomes and events have not been undertaken.