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# MECHANISMS OF DISEASE

## An Introduction to Pathology

*By*

**RUY PEREZ-TAMAYO, M.D.**

*Professor and Director of the*
*Department of Pathology of the School of Medicine,*
*National University of Mexico*

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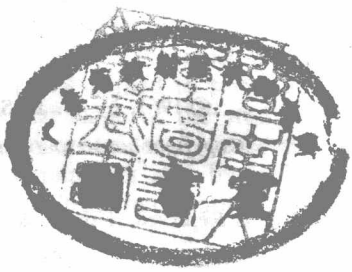

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# PREFACE

The general theme of this book is disease. The central idea, which appears once and again in every chapter, can be expressed as follows: *disease is life under abnormal conditions*. It follows from this concept that an adequate understanding of disease is not possible when studied only from an isolated point of view, as it is also impossible to learn what life is from a unilateral approach. However, didactic requirements impose a dissection of knowledge, in medicine and in any other scientific endeavor. In other words, to reach synthesis, which is the best of all knowledges, it is necessary to analyze. But analysis of facts is only one aspect of the complex process of learning, which can be separated into three different stages; Whitehead has called them the stages of romance, precision and generalization: "The stage of romance is the stage of first apprehension. The subject matter has the vividness of novelty. It holds within itself unexplored connections with possibilities half-disclosed by glimpses and half-concealed by the wealth of material. In this stage, knowledge is not dominated by a systematic procedure. Such system as there must be is created piecemeal *ad hoc*. We are in the presence of immediate cognizance of fact, only intermittently subjecting fact to systematic dissection. Romantic emotion is essentially the excitement consequent on the transition from the bare facts to the first realization of the import of their unexplored relationships. . . . The stage of precision also represents an addition to knowledge. In this stage width of relation is subordinated to exactness of formulation. It proceeds by forcing on the students acceptance of a given way of analyzing the facts bit by bit. . . . New facts are added but they are the facts that fit into the analysis. . . . The final stage of generalization is Hegel's synthesis. It is the return to romanticism with the added advantage of classified ideas and relevant technique. It is the fruition which has been the goal of the precise training. It is the final success." This extensive quotation from Whitehead's *The Aims of Education* finds a direct application in the study of pathology. It may be accepted that this field also goes through three similar stages, which would be (1) the general principles, where the student is presented with a broad view of the mechanisms of disease; (2) the analysis of specific disease entities, and (3) the study of patients, as isolated instances of different ailments. In other words, general pathology, special pathology and clinical medicine. Therefore, the most appropriate introduction to the understanding of disease is the study of the general principles of pathology.

This book was written with the purpose of presenting in a single volume a general survey of the mechanisms of disease. Since it was aimed to serve as a guide during the first stage of the study of pathology it was not considered necessary nor desirable to expand its size by including more data or adding other chapters. For the same reason, it was not limited to the facts obtained by a single method, be it cytologic, histologic, physiologic or biochemical. On the contrary, an effort was made to point out how all these data are integrated within the indivisible whole represented by the human being. In this sense, the book pretends to be more synthesis than analysis, more general than particular, more romantic than precise.

The material consists of two sections

which follow one another in a continuous sequence. The first section refers to the most general aspects of cellular pathology; therefore, it contains information usually treated in texts of general pathology. The second section has been arbitrarily selected from a much larger group of subjects and its purpose is to present a coherent view of disease as a disturbance in homeostasis. A growing body of information suggests that "The coordinated physiological processes which maintain most of the steady states in the organism . . ." belong to the general group of self-regulatory or "feedback" mechanisms. From the formation of adaptive enzymes to the regulation of posture, the principle seems to be an incipient failure in performance that tends to cancel itself. Disease, and many of the clinical manifestations of abnormal processes, are considered to be uncompensated disturbances of self-regulating mechanisms which bring about a loss of homeostasis. These concepts are enlarged in the Epilogue, where the nature of disease is explored with more detail and in a more philosophical vein.

Each chapter is followed by a list of references to the literature which will surely reveal the personal interests and biases of the author. An effort was made to document most of the important statements and to include those recent references examined personally which contain long bibliographical lists. It is customary to offer an apology to those authors whose work has not been included in the bibliography, and the present writer has no wish to break the custom. For that reason, the apology is here most humbly offered. But at the same time it is true that most of the publications left out were considered inadequate or were simply not consulted; the human brain, as the physical facilities of libraries, has limits that cannot be trespassed, and if these limits are added to the tyranny of time and the immensity of present-day literature, this fault of the book may be understood. Indeed, art is long and life is short.

## ACKNOWLEDGMENTS

This book is an abridged adaptation of my "Principios de Patologia," published in Spanish in 1959. I have availed myself of the opportunity presented by this English edition to review the text, introduce new figures and bring the references up to date. It is a pleasure to acknowledge that, both for the Spanish and for this edition, I have been privileged with the generous and valuable advice of my friend and associate Dr. Herman Brandt, who cheerfully released me from most of my administrative and academic chores during the long months occupied in completing the text. It is no reiteration of a worn-out habit to state that without his help the book would be still in preparation; furthermore, several chapters were carefully reviewed and courteously but rigidly criticized by Dr. Brandt, thus eliminating many flagrant mistakes. That I did not always follow his worthy suggestions is something that both the reader and I may rightly regret, and that makes all inaccuracies and obscurities my sole responsibility. Dr. Luis F. Bojalil revised his section on Chemotherapy for this edition, and both to him and to Dr. Francisco Biagi I am grateful for contributing with their specialized knowledge on the host-parasite relation. Dr. Irmgard Montfort and Dr. Marcos Rojkind made many suggestions for the chapter on Connective Tissues and kindly obtained some bibliographical notes. I am grateful to Drs. Amado González and Juan M. Gutiérrez Vázquez for thoughtful and informative conversations and discussions on my brief and amateurish excursions into medical history and philosophy contained in the Introduction and, above all, in the Epilogue. For the selection of illustrations my thanks and deep appreciation belong to Drs. Fernando Flores Barroeta and Luis Salinas. Many authors and editors gave permission to use published material, and although this is recognized at the appropriate places I would like to leave record here of my gratitude for their kind courtesy. Drs. Edmundo Rojas and Edward S. Murphy lent me some valuable specimens for illustration of uncommon conditions. The credit

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for photographic work belongs to Mr. José Bautista, photographer to the Department of Pathology in our school, who has always responded to the most exacting demands.

The Spanish edition of this book was dedicated to my wife. It is at her prompting and with her authorization that the present edition is dedicated to my teachers. It is obvious that the list contains the names of some of the most distinguished pathologists and scholars of our times, but it has not been included for the purpose of presenting their authority as an excuse for my limitations. On the contrary, I am eager to state the specific reasons for mentioning their names. Dr. Isaac Costero introduced me to pathology and inspired an intense devotion to science and a great love for teaching, which at best can only be a pale reflection of the same qualities admired in him by the many generations of fortunate students that have come under his influence; in addition, his friendship and guidance in scientific and many other fields are here most gratefully recognized. Dr. Lauren V. Ackerman unveiled the privileged role of the pathologist in clinical medicine and generously gave me of his immense experience in tumors. Dr. Gustave J. Dammin personifies the synthesis of physician and investigator which should be the goal of all those interested in the healing arts; his friendship is one of my most treasured affections. Dr. Averill A. Liebow may be a little surprised to see his name in the list of my teachers, since my association with him was only too brief; nevertheless, in that short period I was deeply impressed with his scholarship and Olympian passion for truth, so I must beg his indulgence for my undeserved wish to be his student, and his forgiveness for listing his name with those of my other teachers. Dr. Robert A. Moore was one of the best teachers it was my fortune to work with, and I will always be grateful for the many "pearls" that were casually dropped on my lap. May these scholars receive this humble tribute as a small token of gratitude for what they attempted when I came under their influence.

RUY PEREZ TAMAYO

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## PART II

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# INTRODUCTION

The word pathology means "branch of Medicine which studies diseases and the disturbances produced in the organism." It is, next to Therapeutics, the oldest division of the healing arts. According to Krumbhaar,[1] the term pathology "might be thought a more suitable name for our profession than 'medicine,' which presumably conquered through its euphemistic emphasis on the idea of healing contained in its derivation." In Spanish-speaking countries, the word pathology requires an adjective to be explicit, such as general pathology, internal pathology, etc., and the same holds for France or Germany. On the other hand, in English-speaking countries, and especially in the United States, the word pathology is usually taken to mean one specific and limited aspect of the entire field, i.e., pathologic anatomy.

The main concern here, however, is not with the word but with the concept; whatever designation is given to this field, the study of the causes, mechanisms and consequences of disease constitutes one of the most important aspects of medicine.

Only a few centuries ago, a sufficiently interested individual could learn most or all the facts of pathology. With time, however, the field became larger and more diverse, so that at present it is well nigh impossible to command it as a whole. Recent advances have been due not only to original contributions of many research workers in pathology, but also to other investigators with interests in associated or widely separate areas such as physics, chemistry, engineering, mathematics, etc. Concepts and techniques elaborated in each one of those fields have found application in the study of disease and have helped to state and/or solve problems that otherwise might still remain either unsuspected or ignored. With this continuous expansion of knowledge, specialization has become necessary. Both the amount of accumulated information and the different research techniques demand long years of study and training, as well as the continuous exercise of special abilities. This is true not only in pure research in biologic sciences but also in the practice of medicine. At the end of many years of training physicians are in danger of finding themselves on the road of those who know more and more of less and less. In order to avoid the negative aspects of super-specialization it is imperative to have a thorough grasping of the general principles of pathology.

The organism is formed by cells which are organized into tissues; the latter form organs, and these become associated in different systems. Both ends of this scale are open, since subcellular particles may be further subdivided into molecules and atoms, and man is only part of social groups of different sizes. Each level of organization has its own reactive features in disease, so that the study of pathology at a given level provides data which cannot be obtained nor replaced by information derived from higher or lower levels. Historically, the development of knowledge in pathology has gone from gross to microscopic changes, and is now moving into the submicroscopic and molecular levels. The study of such evolution is of interest not only in itself, but also because "nothing gives a better perspective of the subject than an appreciation of the steps by which it has reached its present state."

The historical growth of pathology can be considered in four broad stages, each one


FIG. 1. Antonio Benivieni.

HIERONYMVS BENIVENI, VS IOHANNI ROSATO ME DICO ET PHILOSOPHO .S.

VM POST Inſperatã aman
c tiſſimi fratris mortẽ, qua, prop
terea q̃ quicquid in me fugiẽtis
uitæ ex tam multis miſeriis ac langoribus
ſupererat, uno illo niteretur, nihil mihi in
terris potuit accidere grauius, cius per q̃
ſane honeſtam &omni doctrinaꝝ genere lo
cupletem bibliothecam euoluerem, incidi
in pleraq̃ eius ingenii monumẽta: quæ ille,
ut erat uir doctrina & ætate proiectior, ac
propterea multaꝝ rerum uſu & experientia
pollens, cudebat quotidie. Lectitanti igit̃
ea mihi, ac ſæpius ob memoriã illius reuol
uenti obtulit ſe ſe interea libellus quidam,
in quo uir fũmo & ſtudio & diligentia præ
ditus, q̃cunq̃ trigeſimum ſupra ſecundum
iam annum medenti illi admiratione digna
occurrerant, & ex quoꝝ cognitu uſus aliqs
poſſet exiſtere, ſtudioſiſſime prout quæq̃ ac
ciderant ſcriptitabat. Delectatus ſuꝫ fateor
nouitate ipſa rerum & uarietate lectionis:
Measq̃ partis eſſe duxi, ea q̃libet impolita,
et quæ tumultuaria quadam, ut uidebañ,
feſtinatione ex tempore potius effuſa, q̃ a cu

a ii

FIG. 2. First page of Benivieni's Book.

highlighted by a fundamental change in the idea of the seat of disease. Such stages may be labeled humoral, organic, tissue and cellular; the present times will probably be known to posterity as the beginning of the subcellular epoch.

**A. Humoral Epoch.** The beginning of the development of pathology extends from the earliest records of history to the fifteenth and sixteenth centuries, when the spirit of the Renaissance shook the Western World, creating among other things the freedom necessary to doubt the dogmatic authority of Galen without imminent danger of dying at the stake. Theories dominating this stage of knowledge were adopted from India and Egypt by the Greeks and were based on "spirits" and "humors." It is very difficult to give even an approximate idea of the complexity and fantasy of these theories, not only because at present it seems incredible that they were ever considered true, but also because they changed from one place to another according to popular folklore (*see* Epilogue). The study of anatomy was begun in the sixteenth century and this can be considered as the declination of "humoral" pathology, notwithstanding the heroic defenders of the same type of hypotheses which, more or less disguised, have been advanced during the twentieth century.

**B. Organic Epoch.** Most medical historians agree in considering Antonio Benivieni[2] (ca. 1440–1502) as the father of pathologic anatomy (Fig. 1), with that curious tendency to view the different branches of science as the sudden result of the work and vision of one man. Nevertheless, his book does appear to be the first dealing with anatomic changes in the different organs in relation to clinical symptoms. Benivieni lived in Florence, in the same picturesque epoch of Lorenzo de Medici and Machiavelli, dedicated to the practice of surgery. His observations would have remained unpublished had it not been for his brother Hyeronimus, who five years after Antonio's death collected all his writings and published them under the title *De Abditis Nonnullis ac Mirandis Morborum et Sanationum Causis* (Fig. 2). This is a most fascinating and charming document of the status of medicine in Italy in the early Renaissance,[3]

full of interesting observations dealing not only with pathology but also with the practice of surgery and life in general. It contains the protocols of a little more than fifteen autopsies, performed with the purpose of ascertaining the seat of disease or the cause of death. There is in addition a short description of the clinical illness, in each case, but in most of them both the history and the autopsy findings are too brief to allow interpretation at a distance of four centuries. A good example of Benivieni's work is Case III, "Stones found in the coat of the liver."

"A woman of noble birth had been for long greatly tormented by pain in the region of the liver. She had consulted many physicians, but could not drive out the evil by any remedy. She therefore decided to try my help in conjunction with some others.

"Thus several of us met and discussed at great length from different aspects the hidden causes of this disease. As often happens in doubtful cases, we were divided. Some thought there was an abscess on the liver, others that it was itself diseased, but I personally believed that the fault lay in the covering membrane. A few days afterward the disease took stronger hold and she departed this life, even as we had foretold by common consent from unmistakable symptoms.

"I then had her dead body cut open. There were found in the lower part of the membrane round the liver, a collection of small stones varying in shape and colour. Some were round, some pointed, some square, according as position and chance had determined, and they were also marked with reddish, blue and white spots. These stones by their weight had caused the membrane to hang down in a bag a palm's length and two fingers wide. This we judged the cause of her death and decided that discussions upon what was hidden were vain and futile."

That autopsies were frequently resorted to in order to clarify diagnosis or uncover the cause of death can be surmised by Case XXXII, where Benivieni ". . . was eager to prove this theory by examination and sought to cut open the body, but his relations refused through some superstition or other, and I was unable to gratify my wish," and from Case XXXVII, a boy who died of "callus in the mesaraic veins" and whose autopsy was performed "with his father's consent." Nevertheless, Benivieni was part of his epoch and in his pages exorcisms and demons can be found next to anatomic findings; furthermore, Galen and Avicenna are quoted as maximal authorities.

Benivieni is extremely important in the evolution of pathology not only for his contributions in detail, but mainly because he began the use of a method that has continued to render useful information in the study of disease, namely clinicopathologic correlation.

Of great significance in the development of pathology as well as many other sciences was Jean Fernel[4] (ca. 1497–1558), philosopher, mathematician, philologist and physician (Fig. 3). Fernel was professor of medicine in Paris and in 1554 published his work *Universa Medicina* (Fig. 4) divided into three parts: physiology, pathology and therapeutics. This book was one of the most widely read texts of general medicine in the sixteenth and seventeenth centuries and it passed through more than thirty editions, reprintings and partial translations. The section on pathology consists of seven books divided into 120 chapters; diseases were separated into general and special groups, and the latter were considered under three headings: diseases involving organs placed above the diaphragm, diseases affecting subdiaphragmatic structures and external pathology. From a different standpoint, ailments were also classified as simple, if they involved only part of the organ; composed, if all the organ was affected; and complicated, if the relations between different organs were compromised. Autopsy records were occasionally presented, unfortunately in too brief a form to allow interpretation. This attempt to systematize disease followed a clinical criterion and the anatomic changes of organs were only referred to when related to some sign or symptom.

Early in the seventeenth century there appeared a group of physicians who, instead of limiting themselves to the publication of their own observations, collected all other available experience and printed it in enormous volumes. Most of the time these compilators exercised little or no critical judgment, so in their work it is difficult to distinguish fact from fancy. One of the most important members of this group of early reviewers was Teophilus Bonettus (1620–1671), who graduated from the

FIG. 3. Jean Fernel.

IO. FERNELII
AMBIANI,
Medicina.

AD HENRICVM .II. GALLIARVM
REGEM CHRISTIANISSIMVM.

LVTETIÆ PARISIORVM,
APVD ANDREAM WECHELVM, SVB
PEGASO, IN VICO BELLOVACO.
1554.
Cum Priuilegio Regis.

FIG. 2. TITLE-PAGE OF THE FIRST EDITION OF FERNEL'S 'MEDICINA'.

FIG. 4. Title page of Fernel's *Universa Medicina.*

University of Bologna and early in his career was appointed physician to the Duke of Longueville, a position which allowed much leisure for study. Unfortunately for him, a few months later Bonettus suffered an accident which left him almost deaf and caused him to retire from the practice of medicine. He could then dedicate all of his time to the fulfillment of his cherished ambition: to edit everything that was written up to that time on pathologic anatomy. His efforts appeared in book form in 1679, under the title of *Sepulchretum Anatomicum Sive Anatomia Practica.* This work is made up of 1700 pages and contains protocols of over 3000 autopsies, including those of Benivieni, Glisson, Willis, Vesalius, Riolan, Wepfer and scores of others. The book is important not only because it represents the greatest collection of facts in the entire history of pathology (with the exception of some modern German texts), but also because it served as a basis and stimulus for the work of Morgagni.[6]

The inauguration of pathologic anatomy as a science is marked by Giovanni Batista Morgagni (1682–1771) who started his brilliant career as associate professor of medicine at the University of Padua (Fig. 5). Four years later, however, he moved to the chair of anatomy in the same university and remained there for more than fifty years, loved and respected by all. Morgagni was a retiring, dignified scholar with an almost maniacal love for descriptive detail; a delicate gentleman, he refused to perform the autopsy of his colleague Vallisnieri and of a bishop with whom he had been linked in close friendship. His rare free hours he dedicated to classical culture and archeological studies; most of the time he spent working in anatomy and in clinical medicine. In his later years Morgagni came to be known as "his anatomical majesty," a title more expressive of his prestige than any chronologic list of his achievements.[7] In those times there were no journals in which scientific papers could be published (the present-day deluge of periodicals may make one a little envious of such an epoch) and authors would communicate their findings by means of letters which were read to small groups or scientific societies. When

knowledge had matured enough it was ready to be printed in book form. Morgagni began his work by "sending some letters to my friend. And that he was pleased with them appears from two circumstances; the first, that he was continually soliciting me to send him more and more after that, till he drew me on so far as to the seventieth; the second, that when I begged them of him in order to revise their contents, he did not return them, till he had made me solemnly promise, that I would not abridge any part thereof."[8] Morgagni accepted and in 1761 his monumental work *De Sedibus et Causis Morborum per Anatomen Indagatis* appeared (Fig. 6), containing the clinical histories and autopsy protocols of more than 700 cases. All data, even the most insignificant features of the clinical history and especially of the autopsy findings, are to be found described with great prolixity and unparalleled detail, "without fear of abusing the patience of the reader." At every moment Morgagni tries to establish correlations between morphologic findings and clinical disturbances (there are two indices which list the clinical data with the correlated anatomic findings, and vice versa), thus inaugurating the practice of modern physicians who frequently attempt to express the symptoms in terms of anatomic changes. Morgagni went beyond the explanation of clinical manifestations and "unequivocally committed pathologic anatomic investigations to the revelation of the cause of disease. One can hardly understand why this precise, almost perfectionist scholar should not have recognized the fallacy of this claim. One may find an explanation for Morgagni's apparent conceptual simplicity if one gives thought to the philosophic climate of his period."[9] Klemperer is referring here to David Hume, the Scottish philosopher, whose idea of causality was the continuous association of perceptive data, thus justifying Morgagni's search for the cause of disease in anatomic correlations.

Many interesting observations fill the pages of *De Sedibus;* descriptions of aneurysms, cerebral hemorrhage, ovarian cysts, cirrhosis of the liver, etc., are masterful. The following quotation refers to a patient

FIG. 5. Giovanni Batista Morgagni.

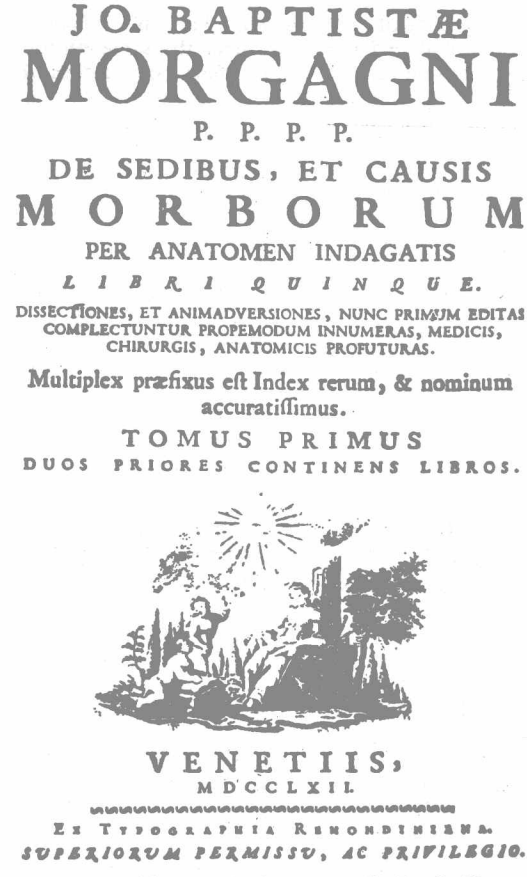


FIG. 6. Title page of Morgagni's *De Sedibus.*

with cirrhosis of the liver, splenomegaly, renal calculi, choroid plexus cysts and an old cerebral infarct:

"An old man of seventy, who had been very voracious in his diet, being seized with an apoplexy long before, and after that with a palsy of the whole right side of the body, was frequently agitated on the other side with convulsions. His senses were affected; and he sometimes discharged calculi with his urine. The abdomen being open'd after death, the omentum was seen to be far drawn upward, as to cover the whole anterior part of the stomach. But the left lobe of the liver, which is us'd to lie over a part of the stomach, scarcely touched it at all, in consequence of being drawn up by the diaphragm, to which it was firmly attached. Moreover, the stomach, although it was corrugated, was, however, when extended, much bigger than it generally is. And the spleen was evidently twice as big as it ought to have been, and of a very dark colour. In the left kidney were found four stones; one of the bigness of a chestnut, the others less. The thorax was not at all open'd. While the brain was taken out of the cranium, some serum, which was contained betwixt the dura and pia mater, flow'd out. In the left ventricle the plexus choroides had in it a body of the bigness of a horse-bean, made up of several hydatids: and under the same ventricle was a sinus, the sides of which consisted of the substance of the cerebrum, that was yellow and flaccid, and seemed also to be corrupted. . ."

Morgagni raised the level of pathologic anatomic description to a degree in which everything described is of value. But Morgagni's eternal contribution is based not only on the scientific facts that appeared in his book, which in themselves would have been sufficient to immortalize him, but on the general principle that organs are seats of diseases and that localization in different organs explains different symptoms. Despite the fact that Morgagni was professor of anatomy, his criterion was essentially clinical and his explanations were humoral. Sigerist[10] pays a fine tribute to Morgagni's genius with the following words:

"From every physician we expect tact and moral earnestness, but we expect them from the pathologist in a supreme degree. It is the dead who are brought to the latter, persons whom medical practitioners have failed to save. All too often an autopsy demonstrates an insufficiency of human knowledge. In such cases the pathologist must not play the part of judge, but must be a helper and an exhorter. It is well that a man of such high character, a man so profoundly impressed with his mission, should have stood on the threshold of the developing science of pathological anatomy."

This stage of knowledge of the science of disease closed with the firm establishment of the principle that symptoms are explained by anatomic alterations, which served as the basis for the fundamental work of Laennec, Bright, Skoda and many other clinician-anatomists of the nineteenth century. In addition, the usefulness of post-mortem studies for the advance of medicine, as a corollary of clinicopathologic correlations, became a more widespread concept throughout the Western World, culminating in the great German school of pathology of the late nineteenth and early twentieth centuries.

**C. Tissue Epoch.** The next great step in pathology was taken by a young French physician, in the most stormy and productive epoch of France. Xavier Bichat (1771–1802) (Fig. 7) studied in Montpellier and Lyon, and was 18 years old at the fall of the Bastille. Bichat joined the army but his poor health did not allow his remaining there for long, and in 1793 he found himself in Paris. Medical schools had been reorganized; Latin had been abandoned as the official language; the traditional division between medicine and surgery was ended; and each "Ecole de Santé" had three hospitals at its disposal and a complete staff of full-time professors with teaching and research laboratories.[10] A protégé of Desault, who was professor of surgery at the School of Paris, Bichat applied himself with tremendous energy to the study of medicine and in 1800, when not yet 30 years old, he was appointed physician to the Hôtel Dieu. Bichat worked day and night in the wards, in the laboratory and in the autopsy room; it is said that in one year he performed more than 600 autopsies, and that his only rest was to change from one type of work to another. Soon the products of such formidable labor began to appear. The one of special interest here was called *Traité des Membranes,* and was published in 1800. In this book Bichat established that organs are formed of elements called "tissu," that similar tissues may form part of different organs, and that this is the reason for the appearance of identical symptoms when different organs are involved. Bichat mentions that there are twenty-one different types of

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