

NEOPLASTIC DISEASES

A TREATISE ON TUMORS

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*FOURTH EDITION,
REVISED AND ENLARGED
WITH 581 ILLUSTRATIONS*

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

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Reprinted September, 1940 and January, 1942

MADE IN U. S. A.

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

To the memory of
JAMES DOUGLAS

A man of ideas, ideals, and affairs

In token of the deep respect of the author

This work is dedicated

PREFACE TO FOURTH EDITION

THE past decade witnessed such notable additions in many departments of the knowledge of neoplastic disease as to call for extensive revision of many sections and complete rewriting of some chapters of this book. Contributions to the literature from the various sciences, physics, chemistry, physiology, and genetics, have greatly increased, and now special treatises are required to deal adequately with these subjects. In general pathology and clinical medicine, the multitude of contributions has been even greater, and the number and scope of the special treatises in these fields have steadily increased and the demand for them has become more urgent. While no single book can fully meet the requirements of specialists in all these fields, the need for a general critical review, as comprehensive as possible and collecting the essential facts and principles in all departments, is probably greater than ever before. In this fourth edition, much old material, mainly of historical interest, has been omitted together with the references; discussions of many debatable tumors have been excluded, and controversial reports have been curtailed—making room for many new contributions of importance. It is hoped that the book is more readable and informative.

JAMES EWING.

PREFACE

It is the object of this work to present within reasonable space and in accessible form the main features of the origin, structure, and natural history of tumors.

Up to a very recent time it has been the prevailing impression that tumors fall into a limited number of grand classes in which the forms occurring in the several organs are so nearly related as to be virtually identical. Hence the practical physician or surgeon has been content to regard all fibromas, sarcomas, or cancers as equivalent conditions without regard to the organ involved, and on this theory to treat the members of each class alike. Upon this theory also it was legitimate to conceive of a universal causative agent of malignant tumors and thus to subordinate many very obvious differences which clinical experience has established in the origin and behavior of different related tumors.

I believe that this point of view has greatly retarded the progress of the knowledge of tumors, and it has been the writer's effort to combat such a conception, so far as present knowledge permits. He has endeavored to analyze the numerous etiologic factors which meet in such diverse fashions in the inception of tumors, to emphasize the general dependence of clinical course upon histologic structure, to trace the histogenesis to the last degree, impressing its essential importance when known, and to enumerate and contrast the more striking clinical features which are often highly characteristic of different tumors.

No one would think of confusing lobar pneumonia with pneumonic plague, although both are examples of acute exudative pneumonitis, but it is quite the rule to identify for statistical studies several equally different forms of mammary cancer. The former diseases are related only as forms of inflammation, the latter only as types of neoplasia. From this point of view it may safely be said that there are more distinct clinical and pathologic entities within the groups of neoplasms than exist outside of them.

While a great volume of information regarding the clinical phenomena of the main forms of tumors is available in special works on medicine, surgery, and the specialties, the task of unraveling their separate varieties, tracing their mode of origin and growth, and establishing the nature of the less common forms, falls to the lot of the pathologist. For the final classification of tumors must depend chiefly on histogenesis and structure. Present-day oncology is chiefly concerned with these topics and the space devoted to them can safely be reduced only when our knowledge is much further advanced.

In spite of several laborious years spent in the task the writer acknowledges disappointment with the results attained in many departments, but can only claim that the effort to present tumors as specific diseases is in the right direction. He first undertook to write a book on the general principles of oncology, but soon found that the significant facts about tumors are not of general application, but are best revealed in the study of special tumor groups or even of special cases.

In the compilation of the work the writer has endeavored to consult with

due respect all the standard authorities, and as far as possible the original contributions in the literature. The rather extensive bibliographic lists seem necessary for the guidance of the reader who desires complete information and to whom the work is chiefly addressed. The recent rapid increase in original contributions from the United States has made it impossible to do full justice to American literature.

It is a pleasure to acknowledge the valuable assistance received from many friends and colleagues here and abroad. The author acknowledges especially his indebtedness to Messrs. W. B. Saunders Company for undertaking the publication of a highly specialized work. Through the painstaking assistance of Mr. William Dunn it has been possible to rely almost entirely upon photographs for illustrations.

While confessing a deep interest in the theoretic problems which render oncology the most complex and fascinating field in pathology, the chief object and hope of the author have been that by rendering more accessible to English readers the knowledge of tumors he may contribute something toward the reduction of the mortality from cancer.

JAMES EWING.

CONTENTS

GENERAL ONCOLOGY

	PAGE
CHAPTER I	
HISTORICAL.....	1
CHAPTER II	
DEFINITION. CLASSIFICATION. GENERAL PATHOLOGY.....	9
CHAPTER III	
MALIGNANCY OF CANCER. ITS EFFECT ON THE ORGANISM.....	48
CHAPTER IV	
METASTASIS.....	62
CHAPTER V	
CHEMISTRY OF TUMORS; SEROLOGY.....	75
CHAPTER VI	
THEORIES OF THE NATURE OF CANCER.....	81
CHAPTER VII	
THE SPECIAL ETIOLOGY OF TUMORS; TRAUMA.....	101
CHAPTER VIII	
THE PARASITIC THEORY.....	113
CHAPTER IX	
EXPERIMENTAL CANCER RESEARCH.....	128

SPECIAL ONCOLOGY

CHAPTER X	
FIBROMA.....	156
CHAPTER XI	
MYXOMA.....	182

	CHAPTER XII	PAGE
LIPOMA.....		190
	CHAPTER XIII	
CHONDROMA.....		204
	CHAPTER XIV	
OSTEOMA.....		216
	CHAPTER XV	
MYOMA.....		224
	CHAPTER XVI	
ANGIOMA.....		249
	CHAPTER XVII	
SARCOMA.....		268
	CHAPTER XVIII	
CLINICAL TYPES OF SARCOMA.....		277
	CHAPTER XIX	
SARCOMAS OF BONE AND BONE-MARROW.....		293
	CHAPTER XX	
ENDOTHELIOMA.....		335
	CHAPTER XXI	
LYMPHOMA AND LYMPHOSARCOMA.....		386
	CHAPTER XXII	
TUMORS OF THE BRAIN.....		434
	CHAPTER XXIII	
TUMORS OF NERVE TRUNKS.....		477
	CHAPTER XXIV	
TUMORS OF SPINAL CORD AND MEMBRANES.....		487
	CHAPTER XXV	
GENERAL PATHOLOGY OF EPITHELIAL TUMORS.....		497
	CHAPTER XXVI	
EPITHELIAL AND OTHER TUMORS OF THE BREAST.....		535
	CHAPTER XXVII	
CANCER OF UTERUS, VULVA, VAGINA.....		600
	CHAPTER XXVIII	
CHORIOOMA (CHORIO-EPITHELIOMA).....		625

CONTENTS

xi

CHAPTER XXIX

CYSTS AND EPITHELIAL TUMORS OF THE OVARY.....	PAGE 641
---	-------------

CHAPTER XXX

THE OVARIAN TERATOMA.....	672
---------------------------	-----

CHAPTER XXXI

CARCINOMA OF STOMACH.....	684
---------------------------	-----

CHAPTER XXXII

CARCINOMA OF INTESTINE.....	721
-----------------------------	-----

CHAPTER XXXIII

EPITHELIAL HYPERPLASIA AND TUMORS OF LIVER.....	735
---	-----

CHAPTER XXXIV

TUMORS OF PANCREAS.....	762
-------------------------	-----

CHAPTER XXXV

MAXILLARY TUMORS OF DENTAL ORIGIN.....	768
--	-----

CHAPTER XXXVI

EPITHELIAL TUMORS OF THE SALIVARY GLANDS.....	787
---	-----

CHAPTER XXXVII

TUMORS OF KIDNEY.....	799
-----------------------	-----

CHAPTER XXXVIII

TUMORS OF ADRENAL.....	830
------------------------	-----

CHAPTER XXXIX

TUMORS OF PROSTATE.....	841
-------------------------	-----

CHAPTER XL

TUMORS OF TESTIS.....	854
-----------------------	-----

CHAPTER XLI

TUMORS OF LUNG.....	872
---------------------	-----

CHAPTER XLII

EPIDERMOID CARCINOMA.....	886
---------------------------	-----

CHAPTER XLIII

EPIDERMOID CARCINOMA (<i>Continued</i>).....	933
--	-----

CHAPTER XLIV

MELANOMA.....	948
---------------	-----

CHAPTER XLV

TUMORS OF THE THYROID.....	971
----------------------------	-----

	CHAPTER XLVI	PAGE
THE THYMUS AND ITS TUMORS.....		997
	CHAPTER XLVII	
TUMORS OF THE HYPOPHYSIS.....		1009
	CHAPTER XLVIII	
THE PINEAL GLAND AND ITS TUMORS.....		1034
	CHAPTER XLIX	
TERATOLOGY.....		1041
	—————	
BIBLIOGRAPHY.....		1073
	—————	
INDEX.....		1127

NEOPLASTIC DISEASES

GENERAL ONCOLOGY

CHAPTER I

HISTORICAL

THE Ancients knew cancer well. They treated it by excision and by a variety of escharotics, including the Egyptian arsenical ointment. Cancer is mentioned in the Papyrus Ebers (B. C. 1500) and in the oldest remnants of the literature of India and Persia.

Hippocrates (B. C. 460 to 375) received from earlier days a considerable body of descriptive facts regarding cancer of the skin, breast, uterus, and internal organs, and he first employed the terms *καρκινος* for all indolent ulcers, and *καρκίνωμα* for progressive malignant tumors. The humoral pathology then dominated conceptions of the origin of cancer. Deficiency or excess of blood, mucus, or bile formed the basis of all disease. Herodotus mentions that Democedes (B. C. 520) cured Atossa, the wife of Darius Hystaspis, of breast cancer. Atossa suffered from a *Φῦμα*. The department of Greek of Amherst College has made a thorough study of the applications of this word in Herodotus, and finds that it was used to indicate any chronic growth or swelling. Diagnosis was still probably uncertain when Hippocrates burnt out a carcinoma of the neck, the earliest record of diathermia.

Celsus (B. C. 30 to A. D. 38) distinguished several gross varieties of cancer, and he excised breast cancer, advising against removal of the pectoralis major. Treatment by charcoal was employed by Cato, and a variety of crude internal remedies are mentioned by Pliny.

Galen (A. D. 131 to 203), the founder of experimental physiology and pathology, failed to make any significant advance in the conception of cancer, but the presentation of the humoral doctrine of *atra bilis* in his writings formed a scripture which dominated medical thought for more than a thousand years. Swellings were *secundam naturam* (gravid uterus), *supra naturam* (callus formations), or *præter naturam* (true tumors). The *pneuma*, composed of solid parts and four fluids, blood, mucus, yellow and black bile, ruled the processes of the body. Cancer developed from the concentration of black bile.

Suppression of menses and hemorrhoids, preventing the discharge of black bile, were chiefly responsible for cancer, which appeared where the bile gravitated in face, lips, breast, etc. No modern writer has been able to reflect the thought of that period or to explain the firm entrenchment of the crude humoral theories. Since capable logic could not have been lacking, one must suppose that religious and esthetic tendencies in the race unfitted the human mind for natural thought regarding the structure and functions of the human body. For internal cancer, of which little was known, a diet chiefly vegetable was recommended. Walnuts were specifically forbidden.

Diagnosis rested chiefly on the supposed cause of the disease, while treatment by excision, ligation of vessels, and cautery was comparatively successful.

Leonides of Alexandria (A. D. 180) broke away from Hippocrates' conservatism, dissected out breast cancer extensively, cutting through healthy tissue with knife and cautery, and approached closely to the modern technics of this operation.

In the Byzantine period (475 to 1500) considerable progress was made in the description of various tumors. Paulus of Æginia (625 to 690) separated chronic metritis from uterine cancer. In Arabia, Avicenna (980 to 1037) introduced the internal use of arsenic, and Avenzoar (1070 to 1162) employed the esophageal sound and the nutrient enema. The 13th to 15th centuries were the Dark Ages for medicine, and especially for surgery. At the Council of Tours (1162), and later, at the Fourth Lateran Conference, the ban of the Church was laid upon the free pursuit of surgery. The fact that surgery could be studied only in private and practised only by nomads was possibly both cause and effect of these ecclesiastic orders. At the Universities of Salerno and Montpellier (1150) the Church designated what books should be used. The Monks jealously dominated medical speculation and concerned themselves mainly with translations of the classics. Walsh would defend the influence of the Popes of this period on science, and refers to publications on anatomy and surgery from Catholic schools where these branches of learning were undoubtedly cultivated. Lanfranchi, of Lyons, an exile from Mailand, established scientific surgery in France (1290) with two notable works. He strongly urged the radical operation for cancer with free bleeding of the affected part. Henri de Mondeville and Guy de Chauliac (1300 to 1368), physician to Clement VII, wrote text-books on surgery, excised cancer with the knife, and developed to a high degree extirpation by caustic arsenic. Yet the Medicine of the Monks must be rated as unfruitful, and as incompatible with the progress achieved shortly thereafter in the Renaissance.

The Renaissance (1500 to 1700), bringing the discovery of the printing press and the circulation of the blood (Harvey, 1628), greatly facilitated the spread of knowledge, and aided the more accurate diagnosis and better treatment of cancer, but threw little light on etiology. Andreas Vesalius (1514 to 1564) began the attack on many of the concepts of Galen, identifying deep-seated with ulcerating cancer. Fabricius (1537 to 1619) separated many inflammatory swellings from cancer, warned rigidly against incomplete removal, extirpated the uterus, and experimented with internal remedies.

Marcus Aurelius Severinus (1580 to 1656) described myxosarcoma, separated cancer from benign tumors of the breast, and extirpated the axillary nodes.

In Prag, Sennert (1572 to 1637), and in Lisbon, Lusitanus (1642) first claimed that cancer was contagious, a doctrine which prevailed extensively and with little dissent. Paracelsus (1493 to 1541) stands out as the first successful opponent of Galen's theory of *atra bilis* as the cause of cancer. He claimed that the disease was due to mineral salts in the blood. He seemed to think that cancer developed where various animal salts became concentrated and sought an outlet. At this period it is interesting to note that the decline of Galen's authority, and distrust of even his crude theories of etiology led to complete demoralization in the treatment of cancer, encouraged great abuse of arsenic and other internal and external remedies, permitted the faith-cure career of Queen Elizabeth (1602), and developed many fantastic theories regarding the nature of cancer.

The Lymph Theory.—In the 17th century Galen's doctrine was completely demolished by the discovery of the circulation by Harvey (1628), of the lymph-vessels by Olaus Rudbeck (1652) (Haeser), and of the red blood-cells by Malpighi (1661).

Malpighi used the microscope which had been in existence since 1529. The black bile was nowhere to be found, but everywhere was blood and lymph. Lymph coagulated and foamed on boiling, hence cancer was composed of lymph varying in density, alkalescence, or acidity, and in malignant tumors fermenting and degenerating. Louis (1723 to 1792) distinguished gelatinous lymph (goiter) and albuminous lymph (scirrhus). LeDran (1685 to 1770) studied cancer by many autopsies, emphasized the local nature of cancer of the skin, and the internal origin of breast cancer. He conceived that if a drop of cancer lymph passed the adjacent nodes it contaminated the entire system.

Astruc (1684 to 1766) separated cysts from true tumors, showed that scirrhus and soft cancer were of the same nature, pointed out important differences in prognosis of different types of carcinoma, and by incineration proved that cancer and muscle tissue contained the same salts. Yet he likened the growth of cancer from lymph to the heating and swelling of gypsum in water.

Morgagni (1682 to 1772) established the importance of the pathological anatomy of cancer, describing many internal tumors studied at autopsy, and separating gumma, struma, exostosis, and lipoma from cancer. He distrusted, without replacing, the lymph theory.

A notable event in the history of cancer research was the essay of Peyrilhe (1735 to 1804) submitted to the Academy of Lyons in answer to the question, *Qu' est ce que le cancer?* This was the first systematic investigation of the whole subject and dealt with the cancer toxin, the nature of the disease, the manner of growth, and the treatment. He spoke of the local origin, the production of a specific virus from degeneration of the tumor, and the development of cachexia from this source. He endeavored to demonstrate the virus by injecting tumor emulsion beneath the skin of a dog, but an abscess resulted and his servant drowned the animal. He treated ulceration effectively with the newly discovered *carbolic acid*. His imagination was satisfied by the Cartesian lymph theory of the times.

In Germany the 17th century was occupied by the exploitation of many personal views of the origin of cancer and other diseases.

Chemical conceptions held sway, and cancer was attributed usually to excess of acid, to be treated by alkali (Helmont, Ettmüller).

Stahl (1660 to 1734) supposed that stasis and thickening of the blood were the essential factors. Hoffmann held that life and health depended on normal movements of the tissues; cancer and other diseases resulting from atony, stasis, and abnormal fermentation of blood and lymph. He constructed his anodyne as a panacea to restore tissue tone.

In England, John Hunter's (1728 to 1793) conception of the lymph theory represented a distinct advance toward the cellular pathology. He held that tumors grew from the coagulable lymph constantly thrown out of the blood, that tumor tissue like normal tissue was nourished by the organism and developed according to the same biological laws. In 1802 The Society for Investigating the Nature and Cause of Cancer was formed in London, and formulated the problems of the disease as they stand today. The society dissolved in 1806.

The pathological anatomy of malignant tumors chiefly interested the English observers, and Hey (1736 to 1819) described, in detail, the structure of certain vascular tumors which he found to be composed of organized blood-fluid and a large proportion of lymph, and for which he employed the term "fungus hematodes." Wardrop, 1809, described in great detail miscellaneous tumors of this gross type, attempting to separate them from cancer. Many

of his cases occurred in children, some involved the eye, and one arose from a wart.

Abernethy, 1804, attempted to define the old term "sarcoma" by applying it to various soft tumors, and he called Hey's fungus hematodes "medullary sarcoma." Maunoir, 1820, showed the beneficent result of anatomical study by announcing that each tumor is the result of a morbid change of the fluid or tissue from which it arises, and retains the original characters of this tissue. He employed many crude chemical and physical tests to support this claim.

The close attention then being given to clinical data led Pott (1775) to recognize and describe chimney-sweeps' cancer and to point out its etiology. The English contributions of this period were completed by Home, who, using the microscope, described and depicted rounded bodies which he regarded as lymph corpuscles.

In France, Bichat's studies of tissue structure opened a new era with the appearance of his *Anatomie générale* in 1801. He first distinguished the stroma from the parenchyma of tumors, deriving the former from the originating tissue, and the latter by proliferation from the stroma. Without reliance upon the microscope he regarded the stroma as cellular and conceived of its growth by proliferation.

Following Bichat, Laennec made a systematic study of the gross features of cancer in thin slices, and introduced the term "encephaloid" for the soft parts. Dupuytren attempted to prove the infectiousness of the disease by ingestion and intravenous inoculation of cancer tissue. Bayle and Cayol argued in favor of the constitutional nature of the disease, and fully pointed out the difference between chronic mastitis and cancer.

Broussais's doctrine that cancer was the sequel of recurrent inflammation made some influence on the thought of this period. Based on chemical observation, his claim, that cancer never arises in normal tissues but only after inflammatory alterations, found many adherents and is of interest in connection with later theories.

Lobstein used the term "plastic lymph" and formulated the view that the tumor-forming lymph was not under control of the biological laws of the organism. Recamier studied especially the infiltration of cancer, observed the destruction of veins, and applied the term "metastases" to nodules in the brain in cases of mammary cancer. He recognized the importance of supernumerary organs and nevi as sources of cancer. Andral reflected the confusion of ideas then prevailing by offering his theory that products of secretion became organized into cancer. Cruveilhier regarded cancer as a malignant degeneration which, like inflammation, affected all the organs. Its chief pathognomonic feature was the cancer juice exuded on pressure. Andral thought tumor masses floating in the veins were derived from the fibrin, but Velpeau, in a case of intravenous tumor, searched the blood in vain for cancerous elements. Such questions as the identity of encephaloid or soft cancer with brain tissue were hardly settled. Tubercle was commonly confused with cancer, and gummata imperfectly distinguished from it. Cancers were classified upon crude gross characters, as in Jager's *Handwörterbuch*, Leipsic, 1837, where they were divided into four types, hard, soft, pigmented, and blood-cancer.

Thus, during the sway of the lymph theory, English and French students, while adding important contributions to the descriptive history and gross pathology of malignant tumors, failed to pass beyond the limits of the prevailing theoretical conceptions of the time. It was the great period of individual surmises which in some instances, notably with Hunter, Home, Lobstein

and Recamier, approached closely toward and prepared the way for modern conceptions.

In Germany, Richter, Walther, and others engaged in the current discussions without adding essentially new data.

It was the general conception that the elements of cancer were fluid and traveled in the veins.

Great significance was attached to the observation of tumor masses in the vessels. A special variety of "blood-cancer," supposed to come from irritating elements, was described by Langstaff, 1817, and Carswell, 1834.

Histological Period.—With the construction of the achromatic microscope in Paris, 1824, a new era opened in cancer research. Wolf finds that the first fruitful studies of the structure of vegetable and animal tissues by this instrument were made by Raspail in 1826, who showed that the growth of tissues resulted from the multiplication of cells. He clearly stated the doctrine of the cell, finding that tissues were composed of microscopic vesicles. The structure and growth of fat tissue he described in detail. Collard, 1828, also described rather clearly the stages in the embryonal development of tissues, assuming, however, that the cells originated from plastic lymph. Schwann, 1838, established this doctrine of cellular structure as a universal principle and discovered the nucleus and nucleolus of the cell.

In the same year J. Müller published his classical study of malignant tumors. He found them all to be composed of groups of cells, each containing nucleus and nucleolus. The various current types of cancer he found to be distinguished only by different proportions and groupings of cell masses and stroma. Certain elongated or racquet-shaped cells, "geschwanzten Körperchen," he regarded as on the way to fiber formation, but not as specific cancer elements, which he was unable anywhere to detect. Hence his diagnosis of cancer rested on clinical signs and the anatomical grouping of the cells. He held the interesting view that cancer developed not from normal tissue, but from germ cells which as a "seminium morbi" lay scattered between the tissue elements.

In regard to the origin of the cells it was held that most of them developed from the plastic lymph or blastema by a process of budding. Others resulted from division of nucleus and cell body, or by the transformation of intracellular blastema lying in spaces within the cell body (Virchow's *Bruträume*). The originating tumor-cells were not derivatives of the normal tissue cells, but came from the *seminium morbi*. Hence there were urgent demand and search for specific characters in the tumor-cells. Lebert especially described such specific cells and designated as pseudocancer all tumors, as rodent ulcer, which failed to contain them. Following this principle, Hannover carefully described the group of tumors arising from stratified squamous epithelium and separated them from cancer under the term "epithelioma."

Hannover believed that cancer-cells circulated in the blood and produced metastases as pus-cells produce pyemia.

The doctrine of the specific cancer-cell now became the chief topic of discussion and was supported by many writers. It was opposed by Bruch, who added many details to Müller's work; by Virchow, who found the tailed corpuscles in the normal bladder epithelium; and by Velpeau, who, with Hannover, established the microscopical diagnosis of tumors. Endogenous cell formation then took the place denied the "tailed corpuscle" as the pathognomonic sign of cancer, Bruch, Virchow, Remak and many others accepting the importance of this supposed type of cell growth. The significance of tumor stroma also attracted new attention, especially from Rokitansky, who explained many of the gross features from variations in this element. He also studied

the secondary degenerations of cancer tissue, including inflammation, necrosis, and saponification, and considered the possibility of a spontaneous cure by these processes.

In spite of their very careful histological studies of tumor tissue in the fresh condition, all the authoritative writers of this period including Virchow were led to believe in the origin of cancer from a fluid blastema. Cancer was defined as an organized exudate from the blood with overnutrition and overgrowth. Much controversy arose concerning the various types of blastemas supposed to exist and the changes in the blood from which they were all necessarily derived. Vogel thought there were as many blastemas as tissues, different tumors arising in different tissues according to the type or analogy of the tissue involved (law of analogous blastemas). These views led directly to the conception of cancer as a constitutional dyscrasia (Rokitansky), a belief that gained wide acceptance and seemed to be supported by the anemia of the disease. The help of the chemists was sought to separate from the blood the different blastemas, and Führer was able to distinguish albuminous, chondrinous, and glutinous varieties, each of which gave a suitable color reaction with nitric acid, and which were offered as sources of the corresponding tumors. The idea that exuded elements of the blood could become organized into cancer was vigorously opposed by Cruveilhier, who urged that extravasated blood never became organized, but had lost all claim to vitality. Cancer could therefore develop only in the vessels. This reasoning led Langenbeck to study cancerous masses in the veins which he found to be composed of fibrin, pus-cells, and cancer-cells. He, therefore, drew the important conclusion that cancer-cells possess a remarkable capacity for independent existence and that they were carried through the veins, producing secondary tumors or metastases. After Peyrilhe, Alibert (1806) and Dupuytren (1817) produced only suppuration by intravenous injections of tumor emulsion, but Langenbeck, Follin, and Velpeau claimed to have observed tumor nodules in the lungs of dogs receiving intravenous injections. These results, although failing to receive confirmation, seemed then to prove not only the origin of metastases, but the contagiousness of cancer. Yet Bruch at once interpreted them as transportation of cancer-cells and not as infection. He held the lymph-vessels to be the chief channels of transport, and with Meckel described backward transport in lymphatics.

While still burdened by the blastema theory of origin the study of cancer had succeeded up to 1860 in rather accurately describing and classifying the main classes of tumors chiefly according to microscopical structure. The description of the benign tumors, the existence of various types of carcinoma, the malignancy of epithelioma, and the separate position of sarcomas were generally accepted facts. Correct conceptions of the histogenesis, however, were impossible until Virchow founded the cellular pathology upon the doctrine of *Omnis cellula e cellula*. There had been several opponents of the idea that cells could be formed from exuded lymph, notably Cruveilhier, while Remak at the same time with Virchow claimed that cells grew exclusively from other cells by endogenous reproduction; but Virchow applied the new principle rigidly to all departments and especially to the origin and growth of tumors. Coincidentally with this memorable service he fell into two grave errors. He failed to correctly interpret the deceptive evidence of endogenous cell formation and he was led to believe that cancer-cells originated from connective-tissue cells. The latter error he never fully relinquished and possibly on this account his monumental work, "Die krankhaften Geschwülste," was never extended over the field of cancer.

Remak immediately attacked the connective-tissue theory which had