Nineteenth Century Foundations of Cancer Research
Advances in Tumor Pathology, Nomenclature, and Theories of Oncogenesis

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SUMMARY
This review discusses morphologic, taxonomic, pathophysiologic, and etiologic advances in nineteenth century oncology. Progress in research on human neoplastic diseases is examined with reference to the origins of experimental research on cancer and related diseases, described in a previous report. A critical bibliography accompanies the discussion.

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INTRODUCTION

"Cancer research, or oncology, is not a science in itself but the simultaneous and frequently coordinated activity of many independent scientific disciplines.... All these approaches have been directed toward the common aim of the elucidation and control of the neoplastic transformation and like all applied sciences are nourished, sustained, and invigorated by fundamental advances and discoveries in these and related fields. They did not start from the same chronologic point, but each, as its usefulness became evident, joined the group which may be called the oncologic sciences (J. P. Greenstein, Biochemistry of Cancer [162])."

This report will outline the formation and early progress of several of the above implicated research trends within the principal clinical schools of the nineteenth century: (a) the English, Scottish, and Irish Schools; (b) the French School; and (c) the German, Austrian, and Swiss Schools. The specific objectives encompass (a) a summary of salient research developments, including a key to the critical literature, in the formative years of modern oncology, and (b) a review of precedents in pre-modern oncology which promoted the realization of experimental programs (405). Crucial research issues will be given emphasis in the text and footnotes.

The organization into geographic divisions, specifically regional schools, does not imply separate modes of thought and influence: the schools were mostly interdependent. Nevertheless, by virtue of a common tongue, each school comprised a unique forum of ideas through its professional societies and prints. Close professional ties also tended to preserve the regional character of research in the nineteenth century. Virchow and Remak were students of Johannes Müller, and Virchow, in turn, educated a succeeding generation of gifted domestic and foreign workers. There are several significant exceptions to this rule; for example, Hermann Lebert (originally Lewy) was a student of many masters and an investigator of truly international proportions. Proper names, professional descriptives, and locations cited in the text are authorized from biographical data in Ackerknecht (2), Wolff (475), Fielding H. Garrison's, An Introduction to the History of Medicine (4th ed., Philadelphia and London: Saunders, 1929), and Haberling, W., Hübotter, F., and Vierordt, H., Eds. Biographisches Lexikon der hervorragenden Ärzte aller Zeiten und Völker (2nd. ed., Berlin u. Wien: Urban & Schwarzenberg, 1929—34).

Problems in nineteenth century oncology did not stand apart from a well established corpus of medical dogma. Thus, theories of oncogenesis, especially before 1850, frequently had to be reconciled to more general pathologic theories; for example, the "humoralist" versus the "solidist" controversy. Views on the local development of cancer have similar historical roots: this thesis was defended by Gendron as early as 1700 (Cancer, 9: 645—47, 1956), yet the dialogue between the "localists" and the "constitutionalists" persisted well into the nineteenth century (110). Indications of circumspect attitudes in the field of neoplastic diseases mark several other significant precedents in the eighteenth century.

ACADEMIC IMPETUS

Peyrère.—Although neoplastic diseases have occupied a prominent place in medical thought from ancient times, interest in the subject began to intensify among medical writers during the eighteenth century (475, 1: 119—122). Additional evidence of this circumstance appears in the stress given cancer research by scientific societies of the period. For example, the French Royal Academy of Surgery in 1732 and the Lyon Academy of Science in 1773 offered prizes for original essays on the question, "What is Cancer?" (115). The latter prize was awarded to the surgeon-chemist Bernard Peyrère in whose work (1774 [306; also 307]) appears the first recorded cancer experiment, the inoculation of a dog with cancer fluid from humans; this is described fully by Woggom (474). Peyrè's study ranks among the earliest to differentiate malignant growths from hyperplasias and benign lesions. For similar observations contemporary with those of Peyrère see Astruc (20) and le Dran (113).

Morgagni.—In 1761 the Paduan anatomist Giovanni-Battista Morgagni published, On the Sites and Causes of Disease (274), in which he laid the foundations of pathologic anatomy on the organ level. Morgagni's work permitted an advance in cancer research by strengthening the conception of cancer as a local disease through descriptions from numerous autopsies of neoplasms at various sites. Morgagni distinguished malignant neoplasms from benign swellings—aneyrums, strumas, gunmas, exostoses, stenomas, etc. This represented a first step toward the later establishment of a sound taxonomic framework for neoplastic diseases.

ENGLISH, SCOTTISH, AND IRISH SCHOOLS

THE SOCIETY FOR INVESTIGATING THE NATURE AND CURE OF CANCER

The first cooperative venture in oncology was promoted by a group of English clinicians who organized themselves into a professional society about 1802. This movement was given impetus by the work of John Hunter, a student of Percival Pott the discoverer of 'chimney-sweeps' cancer. Hunter (1786 [206]) suggested that tumors, although products of lymph secretions, were structurally comparable to normal organ formations, a novel interpretation of the prevailing lymph theory of cancer to which Hunter subscribed. His students and associates, Everard Home (surgery and anatomy), Matthew Baillie (pathology and anatomy), John Pearson (surgery and clinical medicine), John Abernethy (surgery), and Thomas Denman (midwifery), all members of the cancer society, explored the
new avenues suggested by Hunter's conclusion (1, 106, 202, 301).

The English cancer society aroused contemporary interest in cancer by issuing among medical practitioners a questionnaire (1802) published with a glossary in 1806 (316). The brochure covered the following aspects: (a) diagnostic signs of cancer; (b) nature of the precancerous state; (c) relationship between cancer and other diseases; (d) hereditary origins of cancer (e) infectious nature of cancer; (f) local and constitutional predisposition to cancer; (g) climatic and other geographical influences on susceptibility or resistance to cancer; (h) susceptibility of animals to cancer; and (i) spontaneous cures in cancer. Appended commentaries to these questions urged improved clinical observations and diagnostic technics. A reply to the queries was published by the Dublin surgeon Richard Carmichael (1809 [76]) who deemphasized suspected hereditary and infective influences; Carmichael stressed the constitutional source of cancer in terms of an iron oxide deficiency.

Early Surgical Research on Cancer

William Hey (surgery) published in 1803 (191) a series of observations on vascular tumors which he designated fungus hematodes. Tumors of this type were first described imperfectly as spongoid inflammation by the Glasgow surgeon John Burns (1800 [73]), but their relationship to infiltrating cancers of muscle, bone, and blood vessels was explored more thoroughly by the Edinburgh surgeon James Wardrop (1809 [461]). Abernethy (1804 [1]), attempting a classification of tumors according to anatomic structure, described eight types of 'sacroma': (a) common vascular or organized; (b) adipose; (c) pancreas tissue-like; (d) cystic; (e) mastoid or mammary; (f) tuberculated; (g) medullary (identical to the fungus hematodes and later illustrated treatise (1830 [203]) Home indicated homogenous, spherical globules, which he assumed were equivalent to lymph corpuscles, as the structural elements of neoplastic tissues. Sir Astley Paston Cooper (Surgery), through microscopic research, distinguished benign growths and inflammatory hyperplasias, particularly of the mammae (1829 [85]) and testes (1830 [86]), from scirrhoid and other true neoplasms. The pathologist Robert Carswell, by 1838 (77, 78), examined the structure of several widely distributed cancers (i.e., 'scirrhoma' and 'encephaloma'), and he was among the first to suggest the dissemination of cancer through the circulation. Other observations on the morphology of tumors were reported by the pathologist Thomas Hodgkin (1829 [196]) who advanced a cystic theory of tumor genesis which proposed that the production of neoplasms occurred through simple or multiple cysts of unknown character. This hypothesis was criticized by contemporary authors (e.g., Walsh [457, p. 43]) for its etiologic inadequacy.

One of the most comprehensive tumor surveys of the middle period was issued by the Irish pathologist Walter Hayle Walshe who published (1844 [457], 1846 [458]) a tumor nosology in which he correlated previously reported data on gross anatomy with microscopic findings on tumors described by Müller (1838 [280]). Walshe assembled these results into a tumor nomenclature comprising three types of cancer: (a) encephaloid; (b) scirrhous; and (c) colloid. The encephaloid group included Abernethy's medullary sarcoma, the fungus hematodes, and other known varieties of 'soft' cancer. The scirrhous group included Abernethy's pancreatic and carcinomatous sarcoma, and other previously reported 'hard' cancers. The colloid, a new category, included neoplasms which will be mentioned in connection with the research of Cruveilhier and Müller.

Walshe disclaimed contemporary theories which specified trauma, heredity, and chronic inflammation as local, excitary causes of tumors—although he believed that irritation could induce a predisposition to cancer—by suggesting as etiologic alternatives the 'perversion' of nutritive and secretory activities at the intervascular interstices of all organized tissues. This view followed the humoral approach (313; 457, p. 54); however, Walshe's ideas indicate the new trend toward empirical analyses of tumor structure.

In 1849 John Hughes Bennett (39) published data supporting contemporary arguments for structural distinctions among epithelial neoplasms; i.e., between cancers and cancroids as proposed by Lebert in 1845 (233). Bennett admitted that cancroids possessed a 'cancerous nature' but not a 'cancerous structure'; thus he was unable to endorse Lebert's hypothesis on the existence of a pathognomonic cancer cell, a conception advanced simultaneously by Hannover in 1843 (167, 168). Bennett, who held that cancer represented one of many clinically distinct species of destructive growth, contributed to the existing confusion in tumor taxonomy by introducing several artificial distinctions into the cancroid nomenclature—i.e., 'epithelial-cancroid.' He enlarged an alleged category of 'filamentous' or 'fibrous' cancroids to include (a) sarcomatous, (b) desmoid, (c) chondroid, and (d) neumatous varieties.

John Zachariah Laurence (1858 [232]) upheld Lebert's specific cell concept by distinguishing a unique cell type in epithelial tumors, and he supported the claims for Hannover's epithelioma as a local disease distinct from cancer. Between 1847 and 1852 the problem was reviewed by the surgical pathologist Sir James Paget, who greatly assisted the work of bringing order to the systematics of neoplastic diseases. In agreement with Virchow, Paget (1853 [290]) challenged the alleged distinctions between cancroids, epitheliomas, and epithelial cancer by including all within

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3 At this time dogs were thought to be the only species subject to cancer (see 291, p. 167]). The frequent occurrence of mammary tumors (venereal sarcomas?) in dogs was noted by Carmichael (1800 [76, p. 481]). For a review of the English Cancer Society and a reproduction of their report see Michael B. Shimkin, Thirteen Questions: Some Historical Outlines for Cancer Research, J. Nat. Can. Inst., 19: 295-315, 1957.
the same generic category. Moreover, Paget contributed to Virchow's creation of the modern concept of sarcoma by relating description of 'fibro-cellular,' 'fibro-nucleated,' and 'recurrent-fibroid' tumors as a single category, each member of which showed slight structural variations. Paget included in this category the 'fibro-plastic' tumors of Lebert (1845) for which he substituted the term 'myelo-

LATER TRENDS IN TUMOR PATHOLOGY

The impact of more circumspect views resulting from research activities in France and Germany, also influenced the course of English laboratory programs after 1860. For example, in 1850 the surgeon Sir John Simon (382) defined cancer as a neoplasm arising under the pressure of some 'mysterious' constitutional necessity: by 1878 Simon, "reflecting on the present state and prospect of our knowl-

edge of cancer" (383, p. 222), suggested (a) heredity, (b) irritative stimuli, and (c) infective processes as primary causative factors. At the same time he urged the immediate application to the cancer problem of chemical and microbiologic technics.

The scope of the new research is apparent in the work of the Cambridge anatomist Charles Creighton who reported (1874–1876 [95–97]) that secondary and tertiary cancers were not simple offshoots of the parent growth but were autochthonous to the site at which they occurred and resulted from a 'contact-influence' imparted by the primary tissues to the host tissues. Creighton subsequently (1879 [98]) suggested that epithelium infiltrating the surrounding stroma resembled an infective process through which were established autonomous, though reactive (with connective tissue elements) pockets of alveolar cells. This conclusion bridged contemporary views, spearheaded by Billroth, Thiersch, and Waldeyer, on inherent neoplastic alter-

tations in normal tissues. It was also suggestive of early ideas on the induction of tissue alterations in cancer through a pathogenic principle (W. Müller, 1871 [283]).

The idea that epithelioma originated through a prolifera-
tive stimulus in epithelium which had migrated into the connective tissue was similarly supported by Henry Arnott (1872 [18]). Histologic transformations in epithelioma were investigated by George Thin (1876 [402]) who concluded, in agreement with Klebe, that epithelial growth in cancer occurred through an 'apposition' of lymph-cells and preexisting epithelium. The relation of lymphatic tissues in tumor genesis was further studied by George Hoggan (1878 [201]).

Belief in the constitutional (dias thesis) nature of cancer was upheld by Paget (1853 [299, 2: 791–795]) who argued for hereditary transmission. In 1887 Paget (300) expanded this view by suggesting that two coexisting conditions were necessary for the production of cancer: (a) a specific 'morbid' material, perhaps a microbe or virus, which was disseminated through the vascular system; and (b) a hereditary predisposition towards the reception of this neoplastic impetus. The doctrine of the local origins of cancer was defended by the surgeon Campbell de Morgan (1872 [275]) who specified that cancer developed through isolated aggregates of anomalous embryonic cells, derived from neighboring tissues, given a proliferative impetus through irritative influences—a view which adhered to Cohnheim's and Virchow's theories. Conflicting opinions were aired at an extended debate before the Pathological Society of London, March 7th to April 21st, 1874, (110) in which Morgan, Arnott, and others defended the localistic theory, whereas Sir William Jenner, Paget, and Simon upheld arguments for the constitutional theory.

In 1884 the surgeon Sir William Savory (369) reviewed the localist and constitutionalist controversy with reference to newer concepts on hereditary and infectious influences in cancer. He emphasized that the character of cancer in its later stages could differ markedly from its mode of origines; thus, local beginnings and ultimate constitutional manifestations were not incompatible assumptions. Moreover Savory stressed that the role of cells as "immature forms demonstrating pronounced growth lability" be especially considered in tumor pathology. Although the cancer cell resembled embryonic substance in its physi-

cal character, it differed from the latter in its vital attrib-

utes and life history—"in the almost, if not quite com-
plete absence of change of structure or of endowment"—
a distinction of importance for the considerations of tumor taxonomists. In the last analysis, Savory (369, p. 38) conceded that, "before we shall ever be able to answer the question of why or how do tumours form...we must be able to solve the problem of normal growth and de-

development."

The tenor of English cancer research in the 1880's and 1890's, beyond the parasite theory (405, pp. 5–8), generally followed lines suggested by theories on the organic origins of cancer, through (a) irritative stimulus in experimental situations (Power, 1893 [315]) or industrial situations (Spencer, 1890 [388], Marshall, 1891 [263]), (b) through the dislocation of embryonic cells (Spencer- Wells, 1888 [389]) or atypical cell formations (Marshall, 1889 [262]), and (c) through a constitutional or inherited susceptibility (J. Williams, 1880 [471], W. Williams, 1884 [472], Snow, 1885 [384], Butlin, 1887 [74], Woodhead, 1888 [477], Snow, 1893 [385]).

FRENCH SCHOOL

BEGINNINGS IN PATHOLOGIC ANATOMY

The practice of pathologic anatomy instituted by Mor-
gagni was perpetuated in France by the anatomist-physiolog-
ist Marie-François-Xavier Bichat who laid the foundations for histologic research in his Anatomie générale (1801 [41]). In this work Bichat distinguished stroma and parenchyma in rudimentary terms, the former of which he designated a 'cellular system' common to all tumors. Bichat's crude ideas on cancer were substantially im-
plemented (404) by the internist René-Théophile-Hyacinthe

Laennec who classed cancers among the heterologous adven-
titious tissues—tissues which did not have normal organ counterparts but were de novo productions of pathologic processes (1812 [225], also [34]). He listed as representa-
tives of this type (a) tubercles, (b) scirrhus, (c) encephaloid or cerebriform cancers, and (d) melanomas. Laennec (1815 [227]) related encephaloid tumors to the fungus haematodes, medullary sarcoma, and other 'soft' cancers. He also advanced the idea of neoplastic growth as a degenerative process of tissues (226).
Priority for the identification of heterologous tissues was claimed by the surgeon Guillaume Dupuytren (271) who is credited (411) with one of the earlier experimental attempts to prove the infectiousness of cancer by feeding and inoculating animals with fragments of malignant tissues from humans. A similar experiment was performed by Alibert in 1806 (7). The pathologist Jean Cruveilhier extended Laennec's plan of differentiation by devising (1816 [100]) a tumor classification based upon pathological alterations in neoplastic tissues. This development, although it preceded application of the achromatic microscope to the problem, was a decisive follow-up to Morgagni's descriptions of pathologic changes in diseased organs. Cruveilhier defined cancer as a malignant degeneration, as generalized as inflammation, affecting all tissues, and he identified two principal types: (a) scirrhus; and (b) carcinoma (viz. ecephaloides). However, he believed the only difference between these forms stemmed from the relative amounts of 'cancer-juice' occurring in each. Collod cancer, first described by Cruveilhier, was distinguished by him from other neoplastic types since it contained no 'cancer-juice.' By specifying 'cancer-juice' as the common denominator of cancers Cruveilhier's views not only supported the humoral theory (3, p. 117), but also approached the pathognomonic concept of cancer (475, 1: 108).

Although Cruveilhier inclined towards humoralism, Laennec's solidistic outlook was adopted by two internists, Gaspard-Laurent Bayle and Jean-Bruno Cayol (1812 [33]) who investigated the clinical manifestations of cancers and diseases which superficially resembled them; i.e., mammary carcinoma and mastitis, ulcerating skin cancers (long known as Noti me tangere) and intractable ulcerations. They distinguished scirrhus growths from fibroid lesions, cartilaginous and fibrocartilaginous tumors, and melanotic growths. Encephaloid or cerebriform cancers were distinguished from the lesions of tuberculosis and scrofula at various sites. Their diagnoses prompted Bayle and Cayol, in disagreement with Laennec, to argue for the constitutional nature of cancer, a conclusion apparently demanded by the appearances of cachexia and frequent recurrences.

The Vitalist Movement

A countercurrent in the French Clinical School proceeded from the views of the internist François-Joseph-Victor Broussais who opposed the solidism of Laennec by adopting a sthenic doctrine of pathology. The idea that cancer was a manifestation of changes in the constitutional 'tone' or vigor through alterations in the organisms inherent irritability, had been suggested by two English authors (Fearon, 1786 [133] and Nisbet, 1800 [291]). Broussais (1821 [66]) reworked this assumption into the hypothesis that neoplastic growth resulted from chronic inflammation inducing tissue damage through excessive excitation. Broussais supposed that except for superficially localized instances, cancer, as a generalized consequence of inflammation, was incurable, but he also believed that it occurred infrequently since the disease was restricted to a single (inflammatory) mode of origin. Unlike Laennec and Bayle and Cayol who defined malignant growth as an alteration sui generis, Broussais sought its causes in the various pathways of irritation culminating in inflammation.

A modification of Broussais' hypothesis was advanced by the pathologist Gabriel Andral (1829 [9]) who defined cancer not as a specific structural lesion but as a product of nutritive alterations and aberrant secretory activities (designated collectively as lesions of nutrition and secretion) to which inflammation was a contributing factor. According to Andral, cancer was a terminal event, manifesting itself as eroding, infiltrating ulcers, common to a wide variety of nutritive and secretory derangements. He specified the source of cancer 'morbidity' as an organized, coagulated mass of fibrin in the blood stream. This assumption underlay other vitalistic theories of this era, and Andral's views were reflected in Walseh's humoralism. The excitation theory was given a more practical form by the anatomist Gilbert Breschet and the surgeon Guillaume-Marie-André Ferrus (1822 [61]) who attempted to correlate the clinical appearances of cancer with the effects of irritation and inflammation; however, they rejected the nihilism of Broussais by adopting the localistic emphasis upon the early surgical excision of tumors.

The Strasbourg pathologic anatomist Johann Georg Christian Friedrich Lobstein extended the hypothetical consequences of Broussais' doctrine by combining it with Andral's 'blood' theory of cancer formation and other ideas mostly appropriated from Laennec. Lobstein (1829 [240]) proposed that all lesions resulted from a 'plastic lymph,' which, under the influence of a misdirected vital or 'plastic' force, became organized through coagulation and transformation into adventitious (heterologous) formations. Lobstein designated this process as heteroplasia, and he distinguished it from the natural (homeoplastic) capacity of the organism to preserve its original form through regenerative and other growth phenomena. Among the heteroplastic tissues, which were deposited in organ interstices displacing normal tissues (Laennec's definition for degeneration), Lobstein classed (a) scirrho-cancerous, (b) fungus-medullary (viz. Abernethy's 'sacroma'), and (c) melanotic growths. Lobstein's theory was adopted by Astley Cooper and other investigators of the period.

Advances in Tumor Histology

Laennec (227, pp. 169—170) attempted to improve his descriptions of neoplasms by observing macroscopically thin tissue slices, but work in this direction was limited by imperfections in existing lenses for microscopes. Eighteenth century attempts at microscopic examinations, such as by Muys (cited by Louis, 1774 [245]), added few details to a knowledge of tumor structure. In 1824 an achromatic microscope, one of the earliest of its kind, was constructed for Silligues who presented the instrument to the Paris Academy of Science (475, 1: 325). Achromatic microscopes were first applied to the study of plant and animal tissues by Raspail (1827 [320]) and later by Brown (1833 [67]), Schleiden (1838 [370]), and Schwann (1839 [377]). These events are part of the history of the Cell Doctrine. The simultaneous application of the achromatic microscope to the tumor problem by Johannes Müller (1838 [280]) constitutes one of the major advances in nineteenth century cancer research. The availability,
especially after 1860, of reliable fixatives and dyes (e.g., aniline series) for histologic research constitutes another major development (see Epithelial Theory).

Although the Belgian histopathologist Gottlieb Gluge (1837 [154]), using achromatic lenses, reported the appearances of fluids from encephaloid tumors, the work of the histopathologist and clinician Hermann Lebert more closely approaches Müller’s examination of neoplastic tissues. Lebert (1845 [233]) described the form and dimensions of a unique cancer cell which he assumed as the characteristic element of all malignant growths, and he assigned this specific cell type to tumors of a heteromorphic category (comparable to the heterologous and heteroplastic series of Laennec and Lobstein), including the encephaloid, scirrhous, and related forms. Tumors without this atypical element he classed as benign or homeomorphic growths (comparable to the homologous and homeoplastic series of Laennec and Lobstein), which encompassed diverse varieties such as epithelial, fibrous, fibroplastic (sarcomatous), and cystic tumors.

Lebert established a subcategory of homeomorphic tumors, the pseudocancers or cancroids, including ulcerating surface cancers, which otherwise bore a structural resemblance to true cancers except that they lacked the specific, distinguishing cell of the latter—namely, a cell having a distinctive cytologic character. As a consequence of his contention he was forced to deny that cancroids possessed malignant properties. Lebert’s work, continued in later publications (1850 [234], 1851 [235]), advanced the first claims for distinctions in cancer on the cytologic level—Laennec first distinguished cancer on the histologic level—following in the wake of newer pronouncements on the Cell Theory. He arrived at his conclusions from microscopic and physical diagnoses, and in a special work on malignant diseases (1851 [236]) Lebert separated cancers from cancroids in the various organs, designating the encephaloid as a prototype of the former.

Lebert’s specific cell concept was taken up by other French authors of the times (Sédillot, 1846 [379], Robin, 1848 [346]), but it was opposed by the Parisian surgeon Alfred-Armand-Louise-Marie Velpeau (1854 [409]) who, through extensive microscopic diagnoses of neoplastic tissues, was unable to identify a ‘specific’ cancer cell. Velpeau also denied any distinction between cancroids and ‘true’ cancers by stressing that the former possessed the fundamental properties of the latter—the capacity to infiltrate and metastasize. Moreover, Velpeau cited the universal disagreement among microscopists not only on issue of the specific cell but on the entire micrographic record in oncology. For example, Lebert’s report (1852–1853 [237]) on ‘adventitious fibroplastic’ neoplasms was thrown into open controversy (Marjolin, 1852–1853 [261], Follin, 1852–1853 [139])). Follin (1854 [140]) argued for the pathognomonic significance in cancer of atypical nuclei, nucleoli, and other nuclear inclusions, all of which combined to form the distinctive cell character, and he designated this form as nuclear cancer. Courty (1851 [93]) suggested a pathognomonic ciliated cancer cell, resembling squamous epithelial cells, which evolved from preexisting embryonal (cancer) constituents, whereas Broca (1852 [63]), noting the highly diverse structural appearances of

tumors, subscribed to the prevalent blastema theory—the assumption that cells grew out of amorphous matricial or vascular fluid elements.

At mid-century, French investigators, working largely within the framework of the blastema theory, pursued the tumor differentiation problem usually on the basis of homeomorphic and heteromorphic separations (Cruveilhier, 1849–1864 [101], Broca, 1866–1869 [64]). Lebert’s ‘fibroplastic’ tumors were becoming recognized by Robin (1849 [347]), Nélaton (1860 [286])—who described a ‘myoplaxic’ variety—and others, as types of sarcoma. Together with Velpeau, the distinctions between cancroids and ‘true’ cancers were critically examined by Küß (1845 [222])—who was among the first to relate the microscopic appearances of alleged epithelial tumors (cancroids) and ‘true’ cancers—by Michon (1848 [270]), and by d’Hôtel (1855 [204]). Michel (1857 [269]) and Demonchy (1867 [105]) regarded cancroids as true (glandular) epitheliomas. These events coincided with other investigations on the cellular structure of epidermal tumors (Mayor, 1846 [266], Dupuy, 1855 [116], Oilier, 1856 [295], Heurtault, 1860 [190]), although the idea of cancroids as unique cutaneous lesions was not entirely overthrown by 1860.

**Consequences of Histogenetic Research**

As early as 1840 Müller’s discoveries were made known to French medical circles (Mandi [257]). However, the consequences of this new knowledge and its climax in the Cellular Pathology was with few exceptions confronted in France by attitudes still attuned to the blastema theory. Various workers (Lortet, 1861 [242]) accepted Virchow’s contention that cancroids and other cancers originated from undifferentiated elements of the connective tissues. In contrast, Michel (269, pp. 315–339) presented original arguments not only against the specific nature of cancroids, but also conclusions approaching Remak’s that carcinoma was of exclusive epithelial origins. More typical of the period is the work of Robin and his collaborators (1855–1865 [241, 258, 348–355]) on mammary cancers (heteroadenomas). Robin traced the source of ‘heteroadenomas’ to an infiltration and hypertrophy of epithelium. He suggested that although the structure of ‘heteroadenoma’ was analogous to that of normal glandular epithelium, the neoplasms possessed neither the strict appearances nor the same mode of origins as natural acinar tissues. Robin spoke of the pathognomonic character of cancer cells and nuclei, and of a unique form and arrangement of tissue constituents in mammary cancers. Although his ideas were credited by later authors (Herrmann and Lesur, 1885 [187, p. 112]) as a confirmation of the epithelial theory, they were too largely phrased in terms of the specific cell doctrine and the theory of heteromorphic tissues to bring this view into sharp focus.

Following Robin, Cornil (1865 [90]) attempted to demonstrate that the nuclei of acinar cells in tumors became isolated from the connective tissues in the proliferation of neoplasms. Although Cornil (1864 [87–89]), Ranvier (1866 [319]), Demonchy (1867 [105]), and others recognized the exact character of epithelial proliferation in cancer they were unable to relinquish entirely the opinion that epithelial growth originated in the connective tis-
etiologic currents

The nihilism of Broussais appeared in the thinking of Lebert who (234, 236) held that cancer originated through a humoral diathesis overlying some hereditary predisposition; moreover, Lebert viewed the frequent recidivism associated with cancer as proof of its incurability. However, he continued to argue for the local and benign character of homeomorphic tumors such as cancroids. The diathesis doctrine was opposed by Velpeau (1854 [409]) who maintained that cancers arose from local influences—trauma, mechanical insult, contact infection—as well as through hereditary predisposition. To test the hypothesis that cancer was contagious Velpeau, in collaboration with Follin and Lebert, injected human cancer fluids into a dog. This procedure allegedly resulted in the growth of a melanoma at the implantation site (Cornil and Ranvier, 1884 [92]), and the systematical analysis of epithelial tumors was given more detailed consideration by Malherbe (1885 [256]) and especially by Fabre-Domergue (1898 [132]).

The diagnosis and curability of cancer was debated by many high ranking clinicians before the Imperial Academy of Medicine at Paris (1854–1855 [108, 109]). The localists, under Velpeau, were opposed by the constitutionalists under the surgeon César-Alphonse Robert who argued for Lebert's hypothesis. Among other topics the practical value of microscopic diagnoses of neoplastic tissues, specifically form, structure, and pathognomonic significance of cancer cells, nuclei and nucleoli, was discussed. As a consequence, the clinical microscopist and chemist Henri-Marie Delafond presented original cytologic research which severely damaged the specific cell concept.

Delafond's comparative micrometric data on neoplastic tissues from humans and animals (Chart I) led to the following conclusions, translated from the French (1855, 109, pp. 403–405): (a) Normal cells, apart from the embryonic, are entirely analogous in microscopic appearances to so-called cancer cells. It is impossible employing the best microscopes, that is instruments with resolutions of 500 to 600 diameters, to distinguish between these species. (b) In their primordial states, fibroplastic, epithelial and cancer cells show no marked dissimilarities as to form, nuclei, nucleoli, or chemical character. (c) If, later, these three types—particularly fibroplastic and cancer cells—show dissimilarities in form, volume, nuclei and nucleoli, these differences comport with the natural degree of density, fibrousness, softness, or pulpiness of the tumor; micrometric measurements on fibroplastic, scirrhus, and encephaloid cells decisively verify this contention. (d) Free or bound states, form, volume, chemical reactions, and the variable, fluctuating characteristics of nuclei and nucleoli of the so-called cancer cell are of sufficiently marked character to permit positive distinctions between it and the fibroplastic cell. (e) Chemical reactions do not provide the means whereby distinctions between epithelial, fibroplastic, or cancer cells may be adduced. (f) A plentiful number of facts already gathered by skilful microscopists and surgeons adept at experimentation demonstrate that true cancers possess no specific cell, inasmuch as tumors diagnosed certainly as noncancerous present the same cellular aspects as cancerous tumors. (g) Equally undeniable and numerous facts prove that epithelial as well as fibroplastic tumors are true cancers capable of rapid multiplication in situ or at distant sites. (h) These facts demonstrate that the blastema, the morbid principle of cancer, exists as some amorphous entity which eludes our present methods of investigation, and that it is independent for the most part of fibroplastic, epithelial, and those cells
improperly designated as cancerous. Delafond’s counterattack was directed at Lebert (1851, 236, p. 30) who suggested that the mean diameter of the cancer cell ranged between 0.01 and 0.05 mm, except that in encephaloid tumors cell nuclei infrequently exceeded 0.05 to 0.08 mm and were impossible to distinguish from normal cell nuclei. In such cases the nuclei of encephaloid tumor cells appeared defective.

In later years clinical research on cancer reinforced by the Cellular Pathology (of which Bard’s theory is a case in point) broadened the etiologic perspective. The laboratory output resulting from these developments encompasses research on (a) the exact histogenic patterns of malignant tissues (Desfosses, 1881 [107], Ménétrier, 1888 [268], (b) the nature of cancer-cell division (Cornil, 1891 [91], Borrel, 1890—1892 [56, 57], Fabre-Domergue, 1892 [131]), as well as (c) views consonant with Cohnheim’s and Muller’s results, a part of which were reported as early 1830’s [460].

**GERMAN, AUSTRIAN, AND SWISS SCHOOLS**

**Precursors**

Before the discoveries of Müller there were few original opinions on cancer within the German areas. For example, at Göttingen the surgeon August-Gottlieb Richter (1844) in an early 1800 work merely separated ulcerating cancers from scirrhous tumors and he followed the conventional humoral diethesis theory. The Mainz surgeon Carl Wenzel (1815 [469]) distinguished scirrhous from other indurated growths; he thought (469, p. 96) that extensive irritation culminating in chronic inflammation led eventually to the eruption of carcinoma, in indurated tissues. Johann Nepomuk Rust, a Vienna surgeon and a partisan of the localistic theory, argued (1811 [364]) for the existence of an as yet undetermined etiologic moment in the genesis of tumors.

Among early promoters of pathologic anatomy were the pathologist Adolf Wilhelm Otto (Breslau) and the pathologist Phillip Franz von Walther (Bonn), the former of whom (1816 [297]) presented thorough macroscopic descriptions of gastric (alveolar or colloid) cancer. Walther (1820 [459]) devised a classification for tumors which paralleled Laennec’s, and the gross separation of neoplasms among four varieties, (a) soft (Markaschwamm), (b) hard (scirrhus), (c) pigmented (melanotic), and (d) vascular (Blutgeschwamm) continued in the sources of German clinical pathology through the 1830’s (460).

**Blastema Theory**

**Tumor cells.—** The significance of the microscopic investigations (1838 [280]) of the versatile genius Johannes Müller (Bonn and Berlin) has already been indicated. Müller noted the predominance of connective tissue in scirrhous and he differentiated the stroma of adenoid tumors from their parenchyma which he found to exist as a conglomeration of irregular-shaped cells. Müller detected within these cellular aggregates, nuclei, granules, fat bodies, and other inclusions. The occurrence of ‘racquet-shaped’ or caudated cells was also noted by Müller who assumed these to be primordial elements in fiber formation and not specific cancer cells, the presence of which he was unable to establish. With this evidence Müller tried to correlate clinical symptoms with microscopic appearances in diagnoses of cancers.

Müller’s results, a part of which were reported as early as 1836 (279), prompted him to reject the Laennecian concept of heterologous tissues and to adopt a cellular basis for tumor taxonomy. He distinguished according to cell type, (a) fibrous or scirrhous cancer, (b) reticular cancer, (c) alveolar or colloid cancer, and (e) hyaline cancer. Müller also studied the structure of cartilage tumors (echondroma), adipose tumors (cholesteatoma), and cystoid tumors (cystosarcoma) among others. He attempted unsuccessfully to broaden his method of tumor differentiation through efforts to determine solubility differences of neoplastic tissue constituents exposed to boiling water and caustic reagents.

---

**Tableau comparatif des mesures micrométriques moyennes des cellules simples et multiples des tumeurs fibro-plastique, squirrheuse et encéphaloïde de l’homme et des animaux domestiques.**

<table>
<thead>
<tr>
<th>ALTERATIONS</th>
<th>CELULLES SIMPLES ou multiples</th>
<th>HOMMES — DIAMÈTRE.</th>
<th>ANIMAUX — DIAMÈTRE.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DES CELULLES.</td>
<td>DES NOYAUX.</td>
<td>DES NUCLEOLES.</td>
</tr>
<tr>
<td></td>
<td>mm.</td>
<td>mm.</td>
<td>mm.</td>
</tr>
<tr>
<td>Fibro-plastique.</td>
<td>Simple...</td>
<td>0.01 a 0.04</td>
<td>0.001 a 0.004</td>
</tr>
<tr>
<td>Cancer scirrhous.</td>
<td>Id.</td>
<td>0.01 a 0.02</td>
<td>0.005 a 0.006</td>
</tr>
<tr>
<td>Cancer encéphaloïde.</td>
<td>Id.</td>
<td>0.03 a 0.06</td>
<td>0.002 a 0.006</td>
</tr>
<tr>
<td>Fibro-plastique.</td>
<td>Multiples ou mètes.</td>
<td>0.05 a 0.06</td>
<td>0.001 a 0.003</td>
</tr>
<tr>
<td>Cancer...</td>
<td>Id.</td>
<td>0.04 a 0.05</td>
<td>0.002 a 0.004</td>
</tr>
</tbody>
</table>

**Chart 1.**—An example of micrometric research data on cancer and related diseases published in 1854 by Delafond (109). The data show mean measurements on cellular, nuclear, and nucleolar dimensions for human and animal (?) tissues (×600 diameters). The significance of this research is discussed in the text.
(Chemical research on tumors was simultaneously pursued. As early as 1790 Adair Crawford (94) reported chemical observations on the substance of cancer, specifically the elimination of sulfur and ammonia substances from degenerating tumor tissues and their fluids, to which he attached etiologic significance. Routine analyses of tumors appeared in the earlier nineteenth century literature (e.g. Bostock, 1806 [59]). Among these was the 1820 treatise of Maunoir (264) in which the author, utilizing contemporary technics of extraction and sublimation, analyzed with indecisive results the composition of the fungus hematomas. Midcentury chemical research on cancer was typified by analyses for organic constituents, such as appear in Lobstein’s 1829 work (240, i: 403) in which quantitative data for albumins, gelatins, fibrins, and fatty matter in scirrhous tissues were tabulated. Broca (1852 [63, p. 489]) exposed cancer cells to water, alcohol, tincture of iodine, acetic acid, nitric acid, ammonia, ether, and other reagents; he concluded that the walls of these cells had a composition which differed from that of their nuclei. Delafond (1855 [109, p. 401]), through similar experiments, noted that Broca’s conclusion also held for pus cells, epithelial cells, fibroplastic and cancer cells.)

Müller assumed that tumors grew from separate germinal elements within the parenchyma. This idea reflects the blastema theory which was broadly developed in Germany after 1840. Proponents of this theory, from which the specific cell concept emerged, suggested the existence of a unique germinal layer, the ‘cancer blastema,’ through which all autonomous new growths evolved. Concomitant with early developments on the blastema theory, the Danish anatomist Adolph Hanu...
morphogenesis of tumor stromas from the connective tissues. One of the earliest to report in detail on the structural and developmental peculiarities of various cancer stromas, to each of which attached pathognomonic significance, was the Vienna pathologic anatomist Karl Rokitansky (1852 [357]). Rokitansky rounded out these results by special studies on the pathogenesis of villous (adenoid) cancer (1852 [358]), alveolar cancer (1852 [359]), and mammary cystosarcoma (1853 [360]), a neoplasm variously known as the chronic mammary tumor of Cooper and the mammary glandular tumor of Paget.

Tumor nomenclature.—The appearance of new attitudes in taxonomic oncology is evidenced by Müller's work, and this also is part of the pattern of improved knowledge made possible by the blastema theory. Virchow's early opinions on tumor pathology (1847 [412]) show a transition from archaic Laeneccean concepts to the more original outlook: he differentiated among cancers having 'cellular' origins, among cancers having 'fibrous' origins, and among pigmented and vascular cancers. (Later authors adopted similar schemes of classification. For example, August Foerster (1868 [108]) arranged cancers into the following categories, (a) carcinoma fibrosum ('fibrous' cancer), (b) carcinoma medullare ('cellular' cancer), (c) carcinoma telangiectodes, a designation for vascular cancers popular among authors of the period, and (d) carcinoma melanodes or pigmented cancer.) Schuh (1851 [373]) distinguished benign or homeoplastic tumors comprising warty (epidermal), fibrous, fatty, chondrous, osteous, vascular, and muscular growths from various cancers. Bone tumors were thoroughly described by Müller (1843 [281]) and Gerlach (1847-1851 [150, 152]). Rokitansky (1846 [356]) described neoplasms in every known tissue.

Pending more complete histologic data within the total advance of oncologic research after 1840, the tumor nomenclature was beset with numerous arbitrary distinctions. For example, the histologist Jacob Henle (1845 [184, 185]) described a variety of medullary cancer which he designated as siphonoma, although he considered it to be similar to Rokitansky's villous cancer. Villous cancer, the highly vascularized appearance of which was noted by Gerlach (1851 [151]) through examinations of bladder cancers of this type, was considered by Virchow (1847 [412]) to be identical to cystic cancer, first described by Rokitansky (1846 [356, 1: 346-357]) as a cystic, alveolar growth occurring in the gastrointestinal and urogenital systems. Alveolar cancer, was given a variety of names; among others, gelatiniform or gum cancer (Hodgkin), gelatinoma, cancer areolare gelatiniforme (Cruevillier), carcinoma alveolare (Müller), carcinoide celluloides (Vogel), and alveolare Gallereichwech sel (Frerichs, 1847 [143, p. 56]).

The promise of improved identifications of epithelial neoplasms was afforded by the continuing controversy on carcinoids or epithelioma versus cancers or carcinoma. The Berlin internist Friedrich Theodor Frerichs (1847 [142, p. 10]) distinguished the cancer cell as one having, "a tailed and irregularly asteriated form," and the occurrence of other specific forms were advanced by Führer (1852 [149, p. 189]), and Foerster (1852-1855 [135, 136]). This work is part of the expanding research through the 1840's and 1850's on the structure of tumors of epidermal origin (Ecker, 1844-1845 [122, 123]). Bärensprung, 1848 [31], Frerichs, 1846-1849 [141, 144], Bruch, 1849 [69-71], Virchow, 1849-1855 [414, 415, 424, 426], Reinhardt, 1851 [325], Bidder, 1852 [42], Foerster, 1858 [137], Ressel, 1858 [332], Wagner, 1859 [447]) which promoted a gradual expansion of Hannover's narrow conception of epithelioma, arrived at through his limited study of squamous-cell tumors. This research also foreshadowed a complete breakaway of the artificial distinctions between carcinoids and cancers. Thus, Virchow (1855 [424]) confirmed Velpeau's conclusion that both possessed equivalent capacities for metastases and infiltration.

Cellular Pathology

The beginnings of the Cellular Pathology are found in the new emphasis after 1845 on endogenous cell formation. The multitaled pathologist Rudolph Virchow (Wuertzburg, later Berlin), as early as 1847 (412, p. 133), considered it possible that cancer originated not from 'free blastema'—from the intercellular plastic lymph—but from the blastema within pre-existing cells. In a subsequent report Virchow (1851 [420]), starting from the assumption that "a new cell develops within an existing cell," outlined a breeding-space theory which specified that new cell formation occurred under the influence of the nucleus within hollows of the mother cell. By 1855 Virchow (425) had essentially formulated the conception, the details of which comprise his 1858 treatise on the Cellular Pathology (428), that the cell was the focal point of vital phenomena in health and disease.

Although many prominent investigators (Remak, Vogt, Kölliker, and Reichert) joined Virchow in opposing the idea of free cell formation, the actual starting point for the Cellular Pathology—recognition of cell multiplication through division—was a research outcome of the early 1850's even though the process had been observed in the 1840's. For example, in 1841 Remak examined the multiplication through division of blood cells in avian and mammalian embryos. In 1845 he observed the same phenomena in muscle tissues of frog larvae, and by 1851 Remak presented numerous data that every embryonic cell multiplied by division (1852 [328, p. 49], and 1855 [331]). He simultaneously extended the same conclusion to connective tissue cells (1852 [329]). With reference to the earliest work on tumors, Virchow (1857 [427, p. 91]) cited the 1843 observation by Guensburg and Breuer of division in canceroid cells, leading to Guensburg's conclusion (1848 [163]) that all cells were generated endogenously through the partition of their nuclei. At Berlin the adept microscopist Robert Remak, on the basis of initial research in embryology and histology, concluded (1852 [328], 1854 [330]) that germinal cells multiplied through nuclear division to form not only embryonal cells in animals but all normal and malignant tissues as well. Virchow's actual role in these events appears to be negligible (2, p. 76).

Connective tissue theory.—Following in the footsteps of Müller and Rokitansky, Virchow assumed that the connective tissues played an essential role in the formation of tumors. He suggested in 1855 (426, p. 415) that hetro-
plastic neoplasms, including ‘epidermoid’ growths such as carcinoids, originated in the connective tissues. This conclusion, largely derived from various earlier observations by Virchow (see 1853 [422]) on the differentiation of cells within the connective tissues, was supported by similar reports (Pohl, 1855 [312], Senftleben, 1858 [380], Neumann, 1861 [287], Weber, 1864 [462]). It also appeared to be warranted from investigations made by Virchow (1850 [416]), adding to evidence already accrued by Lobstein, on the formation of tumors with combined tissues and on tissue transformations in tumors. The connective tissue theory immediately gained numerous adherents among German investigators in the 1860’s. The connective tissue theory was opposed simultaneously by Remak who held that carcinomas and carcinoids were of exclusive epithelial origins. Beginning with Hannover (1843 [167]), the work of Ecker (1844–1845 [122, 123], Foerster (1858 [137]), and Virchow himself, had led to a clearer recognition of characteristic cell types (i.e., squamous, cylinder, or columnar-cell) in cancers. An indirect argument for the epithelial origins of epitheliomas was stated by Remak (1843–1852 [326–328]) through his embryologic evidence for the existence of three primary germ layers; evidence for these was also furnished by His (1865 [193]). As early as 1852–1854 Remak (328–330) proposed that normal as well as neoplastic epithelial tissues were derived from a separate germinal element. However, Virchow’s authority hindered the acceptance of this “extravagant hypothesis,” as Remak’s view came to be known, until the work of Thiersch and Waldeyer demanded its consideration.

By 1862–1863 Virchow’s ideas on the cellular pathology of tumors were sufficiently crystallized to permit the presentation of an extensive treatment of the subject as a series of lectures incorporated into his treatise, Die krankhaften Geschwülste (431). This study bridged many older and newer perspectives in oncology. Virchow passed beyond the criteria of benignity versus malignancy to include the anatomic and generic relations of tumors in his taxonomic viewpoint. However, he depended largely upon the provisory and arbitrary attitudes on tumors as determined by practical needs, including in his survey of true neoplasms the lesions of tuberculosis, syphilis, and leprosy (2, p. 99). (Die krankhaften Geschwülste which predated the era of microbiology represented a catch-all for every new tissue formation which presented diagnostic difficulties. For example, the inflammatory processes of chronic infection were still poorly understood.) Moreover, the work was never completed. Virchow’s lectures on cancer (carcinoma) were not published, and it is surmised that his doubts concerning the connective tissue theory underlay this omission (2, p. 98; 130).

Virchow (431, 1: 16–32) separated tumors into two major categories: the homeoplastic and the heteroplastic. A tumor differing widely from its matrix-tissue in texture (heteroplasmy) was not rigidly adventitious, nor invariably malignant. Virchow used the term to indicate that in normal circumstances tissues like that of the tumor (a) never occurred at the site in question (heterotopism), or (b) never occurred at the particular stage of development reached at the time in question (heterochronism), or (c) never reached the particular size in question (heterometrism). In one setting a tumor might be ‘heteroplastic’ and harmless whereas in another setting the tumor could be ‘homeoplastic’ and destructive.

After presenting a review of the histogenesis and pathogenesis of neoplasms, Virchow discussed (431, pp. 102–127) a basis for tumor taxonomy according to generic type; viz., (a) through extravasated, transudated or exuded, (b) through secreted, and (c) through proliferative origins. Among the first two classes, designated collectively as cystical tumors, Virchow grouped hematoma (431, pp. 128–154), hygroma (hydrocele, hydromeningocele cerebralis and spinalis) (431, pp. 155–210), and follicular cysts (atheroma and hydatids) (431, pp. 211–286). The third category comprised the proliferative tumors or pseudoplasms which occurred as histoid, organoid, teratoid, or combined forms.

The fibroma (431, pp. 287–363) comprised nodular and papillary growths including the diffuse fibromatoses (elephantiasis). Combinations of fibroid and other tissue types such as ‘epitheloid’ (cancroid) were known to exist, as well as the occurrences of fibroid transformations into sarcomata. These heteromorphic forms, not uncommonly found in bone tumors, were the heteroplastic fibromas. Virchow next discussed hyperplastic, heteroplastic, and multiple lipoma (431, pp. 364–395), followed by a review of the so-called mucous tissue tumors or myxoma (431, pp. 396–434). Chondroma and osteoma were given detailed treatment in other chapters (431, pp. 435–536, also 2: 1–105).

Virchow (431, 2: 106–109) distinguished the psammoma or ‘sand’ tumors from the true sarcoma; glioma and melanoma were also discussed in this section.

The keystone of Virchow’s tumor treatise is the chapter on sarcoma (431, 2: 170–384). Sarcoma comprised a variety of histoid tumors which usually but not always evolved from distinct fibroplastic species such as fibroma, chondroma, osteoma, glioma, etc. Virchow distinguished six major varieties, (a) fibrosarcoma, (b) myxosarcoma, (c) gliosarcoma, (d) melanosarcoma, (e) chondrosarcoma, and (f) osteosarcoma, as well as a number of less specific, local
varieties (e.g., medullary sarcoma). Sarcoma corresponded histologically to the common cellular appearances of normal connective tissues; as spindle-cell, round-cell and star-cell forms. Spindle-cells greatly resembled immature muscle and nerve elements. (Billroth (1860 [47, p. 85]) had suggested from his study of medullary sarcoma that round-cell sarcoma, except for the absence of the characteristic alveolar structure, might be easily confused with carcinoma.) Sarcoma typically metastasized through the circulation especially to the lungs and liver but rarely to the lymph glands. Virchow concludes Volume 2 with chapters on leukemias, lymphomas, and lymphosarcomas (431, 2: 555—756). He is well known for his research on leukemia, a disease which he is the first to have named (1847 [413], 1853 [421]). The history of blood dyscrasias and related subjects are beyond the scope of this report. A partial bibliography of the topic for the interested reader is included in Table 1B.

**Epithelial Theory**

An early countercurrent to the connective tissue theory already has been mentioned in connection with Remak's and Michel's research. Substantial evidence for the opposing view was furnished in 1865 by the Erlangen (also Leipzig) surgeon Carl Thiersch (399) whose investigations on the epithelial origins of epidermal cancers was communicated to the *Congress for Research in the Natural Sciences* at Speyer in 1861 (475, 1: 222). Thiersch acknowledged Remak's three germ-layer principle as the groundwork for the *epithelial* theory.

**TABLE 1A**

**EPITHELIAL (ORGANOID) TUMORS; TUMORS DERIVED FROM MESOBLAST, EPIBLAST AND HYPOBLAST**

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Adenoma</td>
<td>A neoplasm constructed after the type of a secreting gland.</td>
</tr>
<tr>
<td>1. Cystadenoma (multilocular cystoma)</td>
<td>A nonmalignant ovarian adenoma, extensively proliferative, in the composition of which cysts are prominent; occasionally found as papilliferous cystadenomas.</td>
</tr>
<tr>
<td>2. Destructive adenoma (adenocarcinoma)</td>
<td>A highly malignant adenoma, as contrasted with the more localized adenomas of the sweat or sebaceous glands, of the alimentary canal. (A functional rather than a morphologic distinction.)</td>
</tr>
<tr>
<td>B. Carcinoma</td>
<td>A neoplasm essentially distinguished by epithelial multiplication, and not agreeing, or agreeing imperfectly, with a glandular type.</td>
</tr>
<tr>
<td>1. Squamous epithelial cancer (epithelioma; cutaneous cancrum)</td>
<td>A warty and nodular tumor of the skin, characterized by the occurrence of large epithelial nests, made up of large multiform squamous cells which often appear cornified (epithelial pearls); known as horny or corneous cancrum. Cells derived from the superficial epidermis, also the epithelia of the hair follicles and sebaceous glands.</td>
</tr>
<tr>
<td>2. Cylindrical epithelial cancer</td>
<td>A soft nodulated tumor, usually of the mucous membranes, arising from the columnar glandular epithelium; occasionally assumes the appearance of cell-nests as gigantic acini, described as adenocarcinoma (distinct from the term employed for the destructive adenomas).</td>
</tr>
<tr>
<td>3. Simple carcinoma</td>
<td>A neoplasm usually originating in a gland, and forming a rather firm nodulated tumor having a coarse fibrous network, containing alveoli of various sizes and shapes filled with masses of epithelial cells.</td>
</tr>
<tr>
<td>4. Medullary (encephaloid) cancer</td>
<td>A neoplasm having abundant cells and a scanty, delicate stroma, the tissue of which may undergo progressive softening and liquefaction, and from which a milky fluid (cancer juice) may be expressed. Resembles soft adenoma and sarcoma.</td>
</tr>
<tr>
<td>5. Scirrhous</td>
<td>A neoplasm in which the cell-groups are small and scanty and the stroma coarse and dense. Resembles the hard, firm fibromas, and is not sharply divided from simple cancer. The cancer cells often undergo fatty degeneration and are absorbed, leaving a fibrous, cicatricial-like stroma.</td>
</tr>
<tr>
<td>6. Colloid (gelatinous; alveolar) cancer</td>
<td>A tumor occurring as a definite formation or a diffuse infiltration, characterized by a translucent parenchyma (opaque, jelly-like cell-nests giving a glassy appearance) resulting from mucoid or colloid changes affecting the cancer cells. (These changes were studied by Robin, (1853 [348]), Wagner (1860 [448], 1862 [450]), and Schultz (1865 [374]).)</td>
</tr>
<tr>
<td>7. Carcinoma myxomatodes</td>
<td>A tumor occurring as a definite formation or a diffuse infiltration, characterized by a translucent parenchyma (opaque, jelly-like cell-nests giving a glassy appearance) resulting from mucoid or colloid changes affecting the cancer cells. (These changes were studied by Robin, (1853 [348]), Wagner (1860 [448], 1862 [450]), and Schultz (1865 [374]).)</td>
</tr>
<tr>
<td>8. Cylindroma carcinomatodes</td>
<td>A neoplasm which assumes a gelatinous texture in consequence of mucoid or colloid changes affecting the stroma. (Metaplasia of the fibrous tissue is often associated with a simultaneous mucoid degeneration of the cancer cells.) Occasional loss of cell structure through destruction of the connective tissue cells of the stroma. Occurs at the same sites as colloid cancer.</td>
</tr>
<tr>
<td>9. Giant-celled (myeloid) cancer</td>
<td>A rare neoplasm characterized by the formation of homogenous spherules within the cell nests. Cells, compressed by the spherules into slender trabeculae, assume the appearance of an anastomosing network. To distinguish it from the sarcomatous variety, it is designated as carcinomatodes.</td>
</tr>
<tr>
<td>10. Melanocarcinoma</td>
<td>A tumor in which the cancer cells attain enormous size, and become transparent as if through the imbibition of fluids.</td>
</tr>
<tr>
<td>C. Complex or mixed cancers</td>
<td>Combinations of adenoma and carcinoma with other neoplastic formations, resembling simple carcinomas in their general relations.</td>
</tr>
</tbody>
</table>
TABLE 18
CONNECTIVE TISSUE (HISTOID) TUMORS; TUMORS DERIVED EXCLUSIVELY FROM MESOBlast
Based in part on Ziegler’s classification (1885, [480, 1: 199–235]).

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Fibroma</td>
<td>A fibrous tumor. Existing as combined forms (e.g., myxofibroma) (Recklinghausen 1882 [323]).</td>
</tr>
<tr>
<td>B. Myxoma</td>
<td>An edematous (mucus) tumor.</td>
</tr>
<tr>
<td>1. Myxofibroma</td>
<td>A tumor of combined mucus and fibrous tissues, (Koester, 1881 [218], Rumler, 1881 [363]).</td>
</tr>
<tr>
<td>2. Myxolipoma</td>
<td>A tumor of combined mucus and adipose appearances (Virchow, 1865 [430], Waldeyer, 1865 [452]).</td>
</tr>
<tr>
<td>C. Lipoma</td>
<td>An adipose tumor. Existing as combined forms (e.g., myxolipoma).</td>
</tr>
<tr>
<td>D. Glioma</td>
<td>Neuroglia or ganglion cell (?) tumors (Klebs, 1877 [210]).</td>
</tr>
<tr>
<td>E. Chondroma (Echondroma)</td>
<td>A cartilage tumor.</td>
</tr>
<tr>
<td>1. Osseous echondroma</td>
<td>A cartilage tumor involving bone (Virchow, 1875 [432]).</td>
</tr>
<tr>
<td>F. Osteoma</td>
<td>A diffuse and extensive overgrowth in bone (hyperostosis); a circumscribed interior bony growth (enostosis); An independent osteoma remote from bone (hyperplastic osteoma) (Müller, 1858 [278]). Also existing as combined forms (e.g., osseous echondroma).</td>
</tr>
<tr>
<td>G. Angioma</td>
<td>A vascular tumor.</td>
</tr>
<tr>
<td>1. Simple angioma</td>
<td>Simple erectile vascular formation (naevus, hemorrhoid, etc.) (Monod, 1873 [272]).</td>
</tr>
<tr>
<td>2. Cavernous angioma</td>
<td>An erectile vascular tumor in which the tubular form of the vessel is obliterated. Pathologic alterations of a vascular territory; not true neoplasms.</td>
</tr>
<tr>
<td>3. Racemose aneurism, racemose varices</td>
<td>An erectile formation of the lymphatic system comparable to haemic varieties as simple lymphangioma, lymphatic telangiectasis, and cavernous lymphangioma (Anger, 1867 [10], Gyorgjević, 1871 [165], Arnstein, 1872 [19], Wegner, 1877 [465], Nieden, 1882 [290]).</td>
</tr>
<tr>
<td>4. Lymphatic angioma</td>
<td>Tumors of newformed muscle fibers, not unlike fibroma.</td>
</tr>
<tr>
<td>H. Myoma</td>
<td>If fibrous tissue preponderates, the tumor appears as fibromyoma (i.e., uterine fibroids) (Bristowe, 1853 [62]).</td>
</tr>
<tr>
<td>1. Leiomyoma (levicellular myoma)</td>
<td>An unusual tumor rarely composed of striated fibers. Appears in cellular sarcomas as spindle cell forms with striated characteristics (myosarcoma) (Eberth, 1872 [121], Marchand, 1873 [298], Brodowski, 1876 [65], Kocher and Langhans, 1878 [215]).</td>
</tr>
<tr>
<td>2. Rhabdomyoma</td>
<td>A tumor principally composed of newformed nerve fibers (Verneuil, 1861 [410], Bruns, 1870 [72], Perls, 1873 [305], Cserny, 1874 [103], Recklinghausen, 1882 [325]).</td>
</tr>
<tr>
<td>I. Neumma</td>
<td>A growth (lymphadenoma or lymphosarcoma) not strictly a tumor, but a hyperplasia of the tissue proper to lymphatic glands—lymphadenoid (or adenoid) tissue. Relatable to leukemias and Hodgkin’s disease (Lücke, 1866 [249], Langhans, 1872 [311], Mosler, 1872 [276]).</td>
</tr>
<tr>
<td>J. Lymphoma</td>
<td>A tumor of the connective tissues in which the cellular constituents predominate over the intercellular substance. Resemble immature connective tissues, comparable to embryonic forms. Existing as combined forms (e.g., fibrosarcoma).</td>
</tr>
<tr>
<td>1. Round-cell sarcoma</td>
<td>A tumor form common to connective tissues of the locomotive and skeletal systems and lymphatic glands (lymphosarcoma). Related forms: large round-celled alveolar sarcoma and giant-celled or myeloid sarcoma.</td>
</tr>
<tr>
<td>2. Spindle-cell sarcoma</td>
<td>A tumor form with ramified multiform (pyramidal, prismatic, stellate, and irregular) cells; i.e., fibrosarcoma.</td>
</tr>
<tr>
<td>a. Alveolar sarcoma</td>
<td>Sarcoma in which the cell formations resemble epithelial cells or aggregates.</td>
</tr>
<tr>
<td>(1) Plexiform angiosarcoma (endothelioma)</td>
<td>An alveolar formation of the vessels of the brain, lymphatic glands, etc., in which the adventitia is invested with endothelial cells (perithelium) (Neumann, 1872 [289], Kolacek, 1873 [218, 220], Maurer, 1873 [265]). A comprehensive review of lymphangiomas, with complete bibliography, is presented by Glockner (1897 [153]).</td>
</tr>
<tr>
<td>(2) Cholesteatoma</td>
<td>An endothelioma (?) of the pia mater which contains pearly bodies imparting a lustrous appearance, and made up of laminated layers of squamous or tubular cells (pearly tumors) (Lucas, 1873 [248], Wendt, 1873 [467, 468]).</td>
</tr>
<tr>
<td>b. Cylindroma</td>
<td>A formation in which sarcomatous tissues undergo partial hyaline or mucoid degeneration, or when sarcomatous and myxomatous formations combine. The term cylindroma is also applied to tumors of another species in which epithelial cells are involved. It encompasses certain endotheliomas (i.e., myxosarcoma and angiosarcoma myxomatodes).</td>
</tr>
</tbody>
</table>
Thiersch's advance was the result of newly devised technics and circumspect analyses. He attempted to correlate his microscopic findings for normal cutaneous and epithelioma tissues; viz. from differentially stained serial sections prepared through the use of an improvised microtome-like device incorporating a watch-makers saw, as well as through the use of newly discovered dyes and fixatives. He also traced the infiltration of cancer in injected specimens. Thiersch tabulated clinical data on 102 cases of skin cancer from which his histologic materials were obtained. His results are recorded as well in a series of illustrations.

Thiersch established that epidermal tumors were firmly and intricately bound with the connective tissues and that reproduction of their parenchymal elements was usually attended by active stromic growth; however, the specific character of these proliferations remained distinct. This confirmed the idea that ectoderm was deposited as one of the earliest embryonal layers, even though it differentiated into many apparently dissimilar tissues (knowledge of which had been advanced by Kölliker (1863 [221]) and others). Thiersch was able to follow these growth events in the neoplastic alteration, as stated in his conclusions translated from the German: (a) the stroma, although it sustains epithelial growth in a variety of ways, is not the germinal basis of this growth in health or in disease, (b) epithelium possesses its own germinal identity and is the source of distinct formations in health and disease, and (c) it is necessary to alter the thesis omnis cellula e cellula to omnis cellula e cellula ejusdem generis. By extending this research to the subcutaneous glandular (malphigian) layers, the same conclusions were applicable to carcinoma.

Thiersch's work had no resounding impact on medical thought. A critical review of his results was published in 1866 by the Surgeon Theodor Billroth (50),—active at Zürich, then Vienna—whose earlier investigations in oncology (1859 [45], 1860 [46, 48]) led him into Virchow's camp. Billroth cited the substantial amount of collateral evidence thus far gained in favor of the epithelial theory. Nevertheless, Billroth pointed out that Thiersch's data appeared to apply only to a limited number of circumstances. It would be inappropriate and incorrect, Billroth concluded, to extend his arguments to all structures involving epithelial tissues, especially in view of Virchow's weighty testimony to the contrary. For example, how could the epithelial theory account for epithelial tumors in organs which obviously lacked cutaneous tissues—brain, genital glands, etc.? Moreover, primary cancer was known to exist in the tibia and lower jaw, and the possibility of similar occurrences in lymphatic tissues still remained. In the last analysis common, simple cancer was essentially a formation of the connective tissues.

Despite his objections Billroth's opinions were by no means an uncritical vehicle of Virchow's hypothesis. In a paper published simultaneously with the critique of Thiersch, Billroth (1866 [51]) advanced his own views on the anatomy and histogenesis of adenoma and epithelial cancer. For example, glandular (mammary) cancer, which Billroth separated into acinar and tubular varieties, appeared to stem from a destructive impingement of proliferating connective tissue cells upon an actively proliferating adenoid substance.7 This view made concessions...
The assumption that metastases were the possible products of some irradiative, fluid stimulus, an idea similar to that proposed by Virchow. If this type of influence were operative, Billroth conceded, it should have a specific effect, and act in conjunction with cells. The likelihood of contact influences in carcinogenesis would also suggest the presence of an unknown infective agent. Billroth concluded that the problem might be resolved through implantation and inoculation studies in animals of the same species (e.g., melanomas in horses, carcinomas and sarcomas in dogs) since implantations crossing species lines thus far had proven fruitless. He recommended its prosecution to the veterinary laboratories (50, pp. 855-857).

The cancer stroma, the origins of which were traceable to proliferations in the connective tissue regions about the acini, was also examined by Waldeyer who confirmed a number of Rokitansky's observations. Waldeyer stressed that the changing appearances of evolving and evolved stromas, as well as the diverse forms and arrangements of cells of the same stock accounted for many of the difficulties in the earlier carcinoma literature. Lastly, as Thiersch had demonstrated, the distinction between cancers and cancroids was no longer tenable.

**ENDOTHELIAL THEORY**

Despite the accumulation of supporting evidence for the Thiersch-Waldeyer interpretation (Lotzebeck, 1868 [244], Czerny, 1869 [102], Leontowitsch, 1869 [239], Sachs, 1869 [366], Eberth, 1869 [120], Berthold, 1869 [40], Hirschberg, 1870 [192], Hoffman, 1870 [198], W. Müller, 1871 [283], Doutrelepont, 1871 [112], Knoll, 1872 [213], Pérezeserff, 1874 [302]), another theory was beginning to crystallize from the discovery of a 'false' epithelium, the middle-germ layer (motor germinal layer) of Remak, or endothelium. In 1856 Billroth (44, p. 55; 49, pp. 52-53) suggested that vascular tissues through degenerative transformations into hyaline plugs participated in the formation of certain cancroids which he designated as cylindromas. These 'bulb' or 'knob' shaped combination tumors were subsequently studied by a number of investigators (54, 146, 146, 161 (pp. 184-193), 250, 252, 267, 288, 403, 439, 449), and the Strasburg (also Koenigsberg and Wuerzburg) pathologist Friedrich Daniel von Recklinghausen (1864 [322, p. 71]) first implicated the lymph vessels in the development of orbital tumors of this type which he referred to as *myxosarcomas*.

In 1867 Recklinghausen's student Karl Koester (216), through a study of cylindromas of the lower jaw and orbit, substantiated Recklinghausen's contention by proposing that lymph endothelium through cellular metamorphoses gave rise to hyaline (colloid) masses which became reconstituted into the cylindrical cancers; subsequently, Koester (1869 [217]) allegedly traced the development of carcinoma from the endothelium of the lymph spaces. His conclusions were upheld by similar reports on the lymphatic and vascular origins of cylindromas by Pagenstecher (1869 [298]) and Birch-Hirschfeld (1871 [53]), the latter of whom suggested the designation *angioma mucosum proliferum* for this group, and on lymphoadenomas of the pleura and other regions by Ernst Wagner (1871 [451]).
Camillo Golgi, in 1869 (156, 157), first applied the term *endothelio ma* to psammomas of the dura.

The evidence accumulated by Recklinghausen and Koester for the endothelial origins of cancer, supported by similar studies (Ruzitzky, 1874 [365], Rajewski, 1876 [318]), paralleled other results pointing to the formation of cancer from cells of mesodermal origin as muscle (Popper, 1865 [314], Karl Otto Weber, 1867 [464], R. Volkmann, 1870 [440]), cartilage (Karl Otto Weber, 1866 [463]), vessel linings and capillaries (Steudener, 1868 [390], Arndt, 1870 [12], Gussenbauer, 1872 [164], Vajda, 1873 [408]), and from leukocytes (Classen, 1870 [80], Rollett, 1871 [361]). Once again Virchow's arguments for the 'heteroplastic' origins of epithelial tumors appeared to be sustained. Nevertheless, the controversy was effectively offset by adherents of the epithelial theory who countered with fresh evidence.

In Waldeyer's laboratory Carmalt (1872 [75]), using thin sections of freshly extirpated carcinoma which he shook in silver solution, discovered a dissociation of cancer cells from the underlying endothelium which was left intact as a silvered layer. Carmalt thus concluded that endothelium was not necessarily the seat of cancer formation. Furthermore, Carmalt (75, pp. 486-487) was the originator of a culture technic illustrating the amoeboidal movement of cancer cells8 which (a) by contributing to the so-called epithelial infection theory bolstered the Thiersch-Waldeyer conception of metastases, and (b) supported the epithelial theory in conjunction with tissue regeneration studies. The phenomenon of cell motility with respect to cancer had also come under investigation by Classen (1870 [80]) and other workers who postulated the participation of leukocytes in the formation of cancer (Sick, 1864 [381], Klebs, 1867 [209], Schüppel, 1868 [376]). (These views were consonant with the prevalent Waller-Cohnheim leukocyte emigration doctrine of inflammation.) This amoeboidal effect was investigated further by Rollett (1871 [361]), but Biesiaddecki (1867 [43]) showed that migratory white blood cells occurred commonly and without significance among epithelial cells of the outer skin.

Wilhelm Müller (1871 [283]) proposed that cancer cell infectivity stemmed from an undetermined 'virus,' and Friedreich (1866 [148]) reported the occurrence of metastases to a fetus from a primary growth borne by the mother. This event was thought by Friedrich to result from infectious matter in the circulating blood. Waldeyer (454, pp. 83-84; 144-146) argued that speculations on some infective 'virus' were reminiscent of the discredited specific cell concept. He insisted that the epithelial infection theory promoted through the cell motility work of Carmalt and others reinforced the belief in cancer cell propagation through metastases, a phenomenon also established in clinical observations; e.g., Reinecke's report (1870 [324]) on the inoculation of cancer through punctures in peritoneum accompanied by carcinoma.

Another argument raised against the endothelial theory resulted from research on epithelial tissue regeneration by Cleland (1868 [81]), Keller (1869 [183]), Wadsworth and Eberth (1870 [446]), Hoffmann (1870 [200]), Lott (1871 [243]), and others. This work indicated that damaged epithelium regenerated through mitotic activity along its intact edges. Waldeyer (454, p. 80) received these reports as solid collateral testimony for the epithelial theory.

In later years Virchow deemphasized his connective tissue theory (1888 [455], p. 18); 1893 [436, p. 5]), yet it remained part of his views on metaplasia (1884 [434]), and traces of it occurred in his outlook upon neoplastic diseases as late as 1900 (437). He also saw a partial vindication for his beliefs in the endothelial theory.

MODERN FOUNDATIONS OF HISTOGENIC ONCOLOGY

Overwhelming proof for the epithelial theory was brought to bear by Waldeyer in newer, more extensive studies on the pathogenesis of carcinoma (1872 [454, 455]). Through a 5-year study of 203 cases of cancer Waldeyer separated cancers having similar modes of development among five categories: (a) cancers of the outer skin, true epitheliomas and adenomas including the *ulcus rodens*, (b) cancer of cylinder-cell epithelium, of which the alveolar cancers were types, (c) cancers of the acini, a group which included as combined forms the fibrocarcinomas, cystosarcomas, and many other previously described tumors of the mammae, (d) hepatic and renal cancers, stemming from atypical proliferations of the duct linings, (e) ovarian, testicular, and cerebral cancers, a category comprising many tumors of endothelial origin such as the cynthiaomas. Representatives of these in the mesenteries and pia mater were designated by Waldeyer as *plexiform angiosarcomas*.10

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8 Cell motility had been observed by Hoffmann (1868 [199]) as a consequence of contractile phenomena in frog cornea epithelium. It was subsequently studied by Heller (1869 [183]) in connection with cell division in frog tissues. Similar observations were reported by Stricker and his associates in 1870 (see 293, 393). In the light of this research, Carmalt, in the course of excising a carcinoma, collected a quantity of blood from the coagulum of which he obtained drops of serum which were combined with particles scraped from the host tumor. This preparation was examined microscopically under incubation (40°-42°C.), through which cancer cell movement was readily exposed. In more recent times various modification of Carmalt's technic have been applied, especially by Hanes and Lambert (1912 [166]), in a study of isolated fibroblasts from rodent tumors, and by Ross Harrison (1910 [176]) in research on the in vitro culture of nerve fibers. Other forerunners of the modern science of tissue culture (405, p. 29, footnote 17) devised similar methods which, after 1900, gradually gave way to improved techinces (i.e., defined media, balanced salt solutions, etc.) stemming from experimental physiology, embryology, and microbiology.

9 *Ulcus rodens* (cf. basal-cell carcinoma) was long known to physicians as *Noli me tangere*. Bayle and Cayol termed this neoplasm *ulcère cancéreuse*. Lebert, who believed that it lacked the specific cancer cell, designated it *ulcère cancéride*. In 1827 Jacob first referred to it as *ulcus rodens*, and Paget continued to describe it as *rodent ulcer*. Rokitansky and Broca first suggested that it was a growth of epidermal origin, and Thiersch, following this view, classified it as a type of epithelial cancer (475, 1: 211-212).

10 Arnold (1870 [13]) first described a *myxosarcoma telaangietodes cysticum* of the pia mater which Waldeyer (454, p. 137, footnote 3) considered an excellent example of *plexiform angiosarcoma*, a lesion relating the appearances of sarcoma and tumors of the vascular tissues. This was a type entirely comparable to glioma and psammoma. Furthermore, Waldeyer (454, pp. 148-149, footnote 1) related the tumors described by Koester and Recklinghausen to the species of 'medullary' *lymphangionioma* described by Pagenstecher (1869 [398]). Waldeyer viewed these interrelationships as the taxonomic bridge between endothelial tumors and epithelial tumors.
Cancers in organs lacking epithelial tissues unless they existed at epithelial tissue junctures were exclusively secondary productions, an idea contested by Karl Sudhoff (1875 [396]) and others. The endothelial theory, Waldeyer concluded, in no way invalidated the fundamental conditions of the epithelial theory.

Subsequent research in histogenic oncology will be summarized according to the topics, (a) epithelial tumors, (b) endothelial tumors, and (c) connective tissue tumors.

Epithelial tumors.—Pathology texts of the 1870 era (Uhle and Wagner, 1868 [407], Rindfleisch, 1869 [345], Maier, 1871 [254]), still beset by conflicting research results, remained uncertain as to the origins of carcinoma. Waldeyer’s view continued to be disputed through the 1870’s. For example, Schults (1874 [375]) challenged Waldeyer’s critical definition of carcinoma as an ‘atypical epithelial formation’ by proposing instead that the so-called desmoid carcinoma (actually, lymphosarcoma) was an atypical connective tissue formation. Nevertheless, newer investigations (Wolffberg, 1874 [476], Friedländer, 1877 [145], Malassez, 1877 [255], Hauer, 1883 [177], Schuchardt, 1885 [372], Herrmann and Lesur, 1885 [187]) upheld and extended the epithelial theory. After 1900 most pathologists followed Jacob Orth (1904 [296]) in qualifying epitheliomas as tumors having both epithelial cell types and origins. Orth distinguished benign epitheliomas as lesions remaining within the growth-potential of normal epithelium and malignant epitheliomas as lesions transcending this potential. According to Orth, all adenomas were by definition epitheliomas and all malignant epitheliomas were by definition cancers.

Waldeyer, who grossly classified epithelial tumors as (a) surface (cutaneous) and (b) deep-seated (parenchymatous) varieties, was sustained by other authors such as Alberts (1887 [5]) who also insisted that the specific histogenic character of cancers merited them a special taxonomic status. Many systems of classification were suggested through the 1880–1900 period, a late example of which is that by Borst (1902 [58]) who separated epithelial tumors into (a) maturated forms—papillomas, adenomas, cystadenomas—and (b) unmaturated forms—carcinomas.

Many of these tumor classifications, of which Borst’s is an example, incorporated Virchow’s principle of heterotomy as implied in Orth’s above-outlined view. This idea was extensively reworked in the 1880’s as previously mentioned in reference to Bard’s work. According to Bard adult cells, which no longer retained the growth magnitude of embryonic cells, having expended it on the tissue organization, possessed a minimal growth capacity. Referring this conception to the neoplastic series Bard distinguished malignant forms as unmaturated growths—as tissues remaining in the lower stages of development thereby retaining their primitive tendency toward hyperplasia.

This is the principal premise of the epithelial theory. The specific cell concept attempted to define cancer as a unique morphologic entity; as a cell presenting unvarying earmarks. The epithelial theory specified that all cancer cells were atypical versions of normal epithelial cells; not the particular cell but rather the behavior of the group as distinguished through unusual or excessive mitotic figures, aberrant configurations, etc., constituted the morphologic peculiarity of cancer. This not only became the new basis for microscopic diagnoses, but also oriented cancer research toward functional considerations.

Benign varieties, higher in the evolutionary scale, having diverted much of their growth potential into tissue formation, represented maturated species. Bard then adapted this theory to Waldeyer’s views on taxonomy: he distinguished (a) epithelial skin tumors, and (b) glandular epithelial tumors on the basis of maturated and unmaturated representatives within each category. Other workers preferred straight-forward histologic classifications; e.g., Herbert Snow (1893 [385, pp. 28–30]), who separated epithelial tumors into the following groups: (a) epitheliomas (skin cancers), (b) carcinomas (acinar-cell cancer), (c) cylindromas (tubular-cell cancer), (d) rodent ulcer (follicular-cell cancer), (e) lymphocarcinomas (lymph vessel cancer), and (f) blastoma (cancer of vestigial structures, comparable to teratoma). The systematics of epithelial tumors reached its most complex development with Fabre-Domergue (1898 [132, pp. 40–50]). This situation led authors such as Hansemann (1896 [174]) and Lubarsch (1901 [247, p. 229]) to urge a new consideration of Virchow’s less complicated nomenclature. Bard’s attitudes are consonant with theories on the organic origins of cancer which are treated in connection with Cohnheim, Ribbert, and others. Table 1.1A presents in synopsis a taxonomic review of epithelial tumors in vogue about 1885.

Endothelial tumors.—Waldeyer, though at variance with Koester on the origins of carcinoma, acknowledged separable (though relational) taxonomic positions for epithelial and endothelial tumors. Through the 1870’s and 1880’s reports of lymphangiomas and similar formations frequently appeared (Perls, 1872 [305], Schottelius, 1874 [371], Bostroem, 1876 [60], Neelsson, 1882 [285], Baumgarten, 1882 [32], Lubarsch, 1888 [246]). However, new research results in embryology, accumulated as early as 1870 (Goette, 1869 [155], Bambke, 1870 [23]), and especially as a consequence of the later work of Balfour (1880 [22]) and Oscar Hertwig (1882 [188]), clarified the endothelium issue. These investigations demonstrated that mesoderm formation proceeded from the juncture of ectoderm and endoderm at the primitive groove; also, that it split subsequently into a double layer—an outer region which joined with ectoderm to form the somatopleure and an inner zone which joined with endoderm to form the splanchnopleure. The formation of mesenchyme through the fusion of infiltrating mesodermal cells with epithelium also was revealed by these studies. By 1885 it became possible for the investigator to think of two rather than three (Remak-His) primary germ layers.

In the light of this research, Cornil and Ranvier, 1884 [92, 1: 365–374] claimed that endothelium was meaningful only within the context of epithelial formations. His (1882 [195]) advanced the idea of epiblastic, mesoblastic, and hypoblastic tissue formations as phases of development from the archiblasteme as contrasted with development from the parablasteme involving tissues usually identified as endothelial. This concept was elaborated further by Waldeyer (1883 [456, p. 61]), and Klebs (1889 [211]) proposed that it be adapted to tumor systematics; viz., archiblastic and parablastic series. (These conceptions advanced toward improved attitudes on germ layer differentiation in pathologic situations; e.g., see Klaatsch, 1899 [208], Marchand, 1899 [260].)
Many modifications in the nomenclature of endothelial tumors were simultaneously advanced. For example, the Berlin histopathologist David von Hansemann (1897 [175]) held that (a) endothelium and epithelium (angioepithelium) of the vascular and lymphatic vessels, and (b) endothelium and perithelium of the pleuroperitoneal linings, pia mater, and similar structures, were morphogenically synonymous.

Another segment of workers led by Rudolf Volkmann (1895 [445, pp. 12–61]) insisted that cancer and endotheliomas were in no sense embryologically synonymous, although from the standpoint of gross morphology similarities between them existed. Neoplasms of the endothelium were related rather to the connective tissues; in the opinion of Volkmann classification of these tumors should proceed from this assumption. The similarities which appeared to exist between endothelioma and sarcoma, as in the case of Ackermann's (1883 [4, p. 2008]) so-called 'interfascicular' endotheliomas of the serous cavities, strengthened this argument. Moreover, Rozinsky (1896 [362]) reported a transformation of connective tissues to endothelium in ovarian endotheliomas, but this circumstance was doubted by Herz (1899 [189, pp. 462–403]) and other workers. Volkmann's thesis nevertheless tended to undermine Köster's theory which continued to be defended by Mulert (1897 [277]), Glocner (1897 [153]) and others.

A related problem for which a solution also pended involved the category of tumors which passed under the arbitrary designation of cylindroma. Earlier authors were unable to agree on whether cylindromas were carcinoids, sarcomas, or endotheliomas. Waldeyer (1845, p. 132) brought them into connection with perithelial tumors or the pleform angiosarcomas. The alveolar appearance of certain cylindromas as well as their occasional round or spindle-cell appearances, was first described by Sattler (1874 [308, p. 98]) who inferred that cylindroma was a formation of the adventitial tissues (sarcoma carcinomatous). Etwesky (1877 [129]) investigated the processes of hyaline or mucoid degeneration of the fibrous stroma or the adventitia of the vessels in the formation of these growths and he suggested that they be classified according to (a) pure forms existing as plexiform sarcomas and as angiomia mucosum proliferum, and (b) mixed forms existing as plexiform angiosarcomas and combinations of angiomia mucosum proliferum with other new growths.

Despite the intensive research on endothelial tumors by 1900 (475, 1: 287–307) opinions on how to classify them still differed widely. Hansemann who later thought of them as genuine epithelial formations at first suggested (1896 [173]) they be classified within the formal categories, (a) sarcoma, (b) carcinoma, (c) carcinoma sarcomatodes, and (d) adenoma—each suffixed by endothelioma to denote the generic character of the group. Another classification for endothelial tumors having a specific stroma was also proposed by Hansemann: i.e., (a) cylindroma or siphonoma, (b) myoma, (c) chondroma, (d) scirrhous, and (e) mixed tumors capable of transformation into sarcoma or carcinoma. Other authors preferred more homogenous classifications. For example, Amann (1894 [8]), who in agreement with Sattler considered endotheliomas a variety of alveolar sarcoma, suggested they be categorized as (a) perithelioma, (b) endothelioma (intra) vascular, and (c) endothelioma lymphaticum containing the subgroup, endothelioma perivasculare. The question of endothelial tumors remained a prominent research problem in oncology through the early 1900's.

**Connective tissue tumors.—**The later history of research on connective tissue tumors consisted in large part of building upon Virchow's foundations (1850 [418]). Additional histogenetic data on sarcoma were gathered by Billroth and Czerny (1869 [52]), Sokolow (1873 [387]), Tillmanns (1873 [400]), Steudener (1874 [392]), Ziegler (1878 [479]), Ackermann (1883 [4]), and others. Much of this work involved detailed descriptions of special varieties (Gottschalk, 1894 [158], Pick, 1894–1895 [309–311]).

A firm basis for the classification of connective tissue tumors was established by Virchow in *Die krankhaiten Geschwülste* (431, 1: 128–286) through his division of proliferative neoplasms into two major categories; (a) histoid tumors built from tissues of the matrices, and (b) organoid tumors built from elements superimposed on tissues of the matrices and showing complex and variegated characteristics. Cohnheim (1880 [83]) argued that this system advanced morphologic distinctions at the expense of physiologic distinctions: he proposed the establishment of a class of (a) connective tissue types to include fibromas, lipomas, myxomas, chondromas, osteomas, angiomas, lymphomas, sarcomas, and mixed forms (a group comparable to Waldeyer's desmoid tumors—melanoma, myxoma, ependymoma, odontoma, glioma, psammoma and sarcoma; a class of (b) muscle tissue types to include myoma laevicellulare and striocellulare; and a class of (c) nerve tissue types to include neuromas and gliomas.

Cohnheim's system, with its emphasis upon functional distinctions, was subsequently adopted and extended by other authors. For example, Borst (1902 [58, I: 100–509]) also applied his idea of maturated versus unmaturated formations to connective tissue tumors. He grouped benign growths into Cohnheim's category (a), and malignant growths into Cohnheim's category (b) including the destructive sarcomas. Delbet (1896 [104]) followed these general views by distinguishing (a) tumors predicated upon the paradigm of adult tissues, including many harmless histoid neoplasms, and (b) tumors predicated upon the paradigm of embryonic tissues including malignant sarcoma. Table 1B presents, in synopsis, a taxonomic review of endothelial and connective tissue tumors in vogue about 1885.

**Etiologic Considerations**

*Neoplastic blastemas.—*Research on the formation of cancer from atypical blastemas through chemical alterations (e.g., Führer, 1852 [149, pp. 222–224]) tended to sustain the cancer dyscrasia etiology during the blastema era. Thus, Engel (1841–1844 [124–126]) and Rokitansky (1846 [356]) attributed the anomalies of neoplastic 'texture' (stromas) to a blood crisis involving metamorphoses of the blastema. Nevertheless, Rokitansky (356, I:334–335) did not discount the possible local origins of benign tumors, of which he considered sarcoma an
example, through mechanical insult or infection. The
diathesis doctrine was promulgated simultaneously in
Germany by investigators such as Frerichs (1847 [142, p. 7]; 1849 [144, p. 12]). However, Frerichs (1846 [141, pp. 688–690]) indicated that distinctive clinical manifesta-
tions in carcinoma (and tuberculosis) pointed to the
possibility of localized formations of neoplastic pseudo-
plasmata, and that dyscrasia was superimposed in later
stages.

Traumatic and irritative stimuli.—In his tumor lectures
Virchow (431, 1: 41–43, 51, 57–71) proposed a generalized
basis for the generation of neoplastic diseases through
massic organic influences; he also assumed a constitu-
tional predisposition through heredity. However, he had
already become convinced that tumors resulted to a large
extent from local phenomena, through irritative or traumatic stimuli (431, pp. 72–101; 2, pp. 76, 101). The idea
that a local event usually preceded the onset of diathesis
had entered his thinking as early as 1850 (416, p. 135) at
which time he suggested the insinuation of irritative
stimuli in the formation of tumors. (The localized oc-
currence of cartilage tumors as a result of inflammation
and irritation was suggested by von Helmsbach-Meckel in
1856 [267, pp. 62, 78].)

This view was more fully expounded by Virchow in an
1858 paper on Irritation and Irritability (429) in which he
proposed that the specific ‘cause’ of cancer proceeded from
both the nature of the irritative effect and predisposition
of tissues toward this effect. Thus, mechanical and
chemical stimuli were known to induce local eruptions of
new growth in susceptible tissues; according to Virchow
(429, p. 45): “How else is it possible to account for the oc-
currence of the so-called epidermoidal and epithelial
cancer—cancroid—preponderantly at sites most exposed
to mechanical insult; namely, the orifices, the surfaces of
skin, the confines of passages, the lip, the edges of the
tongue, the contact point of esophagous and bronchus, the
cardia and pylorus, the anus, the orificium externum uteri,
the eye lids, and the turbinates of the nose. . . ; moreover,
why does cancroid remain so long stationary where it oc-
curs if it is not a malady of local origins?”

Together with the related problem of trauma, the con-
cept of an irritative impetus toward cancer existed as a
strong current in oncologic thought long before Virchow’s
pronouncement (475, 2: 125–141). Only in the last two
decades of the nineteenth century did the irritation hypoth-
thesis achieve somewhat of an empirical basis from the
laboratory viewpoint (405, pp. 14–15). However, the
irritation hypothesis was sustained through an earlier
recognition of specific environmental stimuli in the
production of cancer.

The frequent occurrence of lip cancers among pipe
smokers was first noted by Soemmerring (1795 [386]), and
similar observations, in which the injurious effects of
tobacco were also suggested, were subsequently reported in
studies on labial cancroids (Lortet, 1865 [242, pp. 52–54]). For example, Thiersch (1865 [399, pp. 190–193])
implicated tobacco smoke and juices in the alteration of
lip tissues culminating in cancer, and he compared this out-
come to scrotal cancers through soot injury in chimney-
sweeps. Similar issues were raised in 1874 at the third

Congress of the German Surgical Association at which the
Leipzig surgeon Richard von Volkmann (441–443) presented three case histories on scrotal cancers in workers of
the coal-tar and paraffin industries. These observa-
tions were simultaneously supplemented by Esmarch (441, p. 6) and Langenbeck (441, pp. 6–7) both of whom sub-
stantiated claims for a statistically higher frequency of
oral cancers among tobacco smokers and chewers. In
1880 Tillmanns (401) examined the ‘tobacco hypothesis’
with the conclusion that smoke tar distillates, particularly
phenol and similar agents isolated by E. Ludwig (1877
[251]), occasioned a neoplastic impetus entirely comparable
to creosote, naphthalene, and other industrial by-products.
These events are a prelude to the discovery of various
industrial carcinogens by 1900, and coincide with the
refinement of clinical observations on the role of trauma
in tumor induction (Volkmann, 1889 [444]).

Senile disposition.—That trauma and related effects
gave only a partial answer to the question of etiology was
generally admitted by 1870. Thiersch and Tillmanns thus
specified that mechanical or chemical influences on the
production of cancer only acted by virtue of a predisposi-
tion rooted in some biologic irregularity. Creighton
(1874 [95, p. 111]) argued that contemporary research as
yet had failed to pin-point the essential character of neo-
plastic growth:

“There is nothing in the explanation of the histogenesis of
the growth [cancer] given by Professor Waldeyer to show wherein
it differs from a mere hyperplasia. Other pathologists, again,
such as Professor Virchow, have been led in the absence of such
an explanation to assign the origin of the epithelial-like cells of
the tumor to an ‘epithelial-infection’ of the connective tissue, re-
jecting, as it were, the strong evidence of epithelial origin for
the sake of being able to account for the hyperplasia of
the growth.”

To fill this gap several hypotheses were advanced,
among the earlier of which is Thiersch’s 1865 theory (399,
pp. 78–86) of senile disposition or growth energy imbalance.
Thiersch conceded that it was necessary to look beyond the
prelusory hyperplasia to find an explanation for neoplasia.
He inferred from his anatomic evidence that aging brought
about senile, regressive alterations of the connective
tissues. Moreover, it appeared that a predisposition
toward cutaneous cancers in the aged proceeded from
epithelial hypertrophy following involution of the stroma.
Thiersch suggested that skin cancers were the ultimate
products of a disturbance in the histogenic energy equilib-
rium between epithelium and stroma. In the face of
diminished stromic resistance, actively proliferating
epithelium established a zone of new growth, continually
pressing its advantage against the stroma, forming the
nucleus of a neoplasm.

Thiersch’s deemphasis of the stroma in cancer formation
was opposed by Virchow’s disciples (Hoebcr (1875 [197])).
Adherents of the epithelial theory were not unanimous in
support of Thiersch’s theory since the concept of senile
disposition did not appear to be universally applicable.
For example, Waldeyer (1867 [453, p. 520]) concluded that
the production of epithelium, contrasted with the inter-
stitial connective tissue, often tended to diminish with
advancing age (e.g., in glandular atrophy); in this case the
epithelial structures tended to lose their proliferative vigor and become subjected to a replacement fibrosis through increased activity of the connective tissue. A further repudiation of Thiersch's theory was issued by Waldeyer in his 1872 work (454, pp. 135–154).

Interface antagonism.—A hypothesis proposed by the Bonn anatomist Franz Boll in 1876 (55) sought to reconcile conflicting views on the growth energy imbalance etiology of cancer. Boll approached the problem of neoplastic growth through attitudes stimulated by Remak's reform of embryology. Since each of the three tissue theories of cancer argued from their own limited and static viewpoints, Boll thought it imperative to refer any problem of growth, as a dynamic process from inception to involution, to the first details of embryogeny. By taking into account newer results in clinical research on cancer Boll's theory had a positive aspect. Its argumentative consistency surpassed many hitherto proposed hypotheses. Nevertheless, his conclusions were opposed by Friedländer (1877 [145, pp. 39–44]) who insisted that Boll's emphasis upon a dual action of epithelial and embryonal connective tissues violated the principle of cancer as an atypical epithelial formation, especially in the light of newer implantation research. (Nevertheless, Friedländer [145, p. 57] conceded that little pathologic significance could be attached to atypical epithelial proliferation of itself; this expressed an already latent realization that some functional basis for atypical epithelial proliferation must be sought.)

Virchow (1880 [433, pp. 192–193]) opposed Boll's reference to the connective tissue germ layer (vascular matrix) as a "tissue reverted to a condition wholly analogous to the embryonal," he claimed that this expressed nothing more than his own idea of an 'undifferentiated granulation tissue' as the starting point for cancer. Virchow also criticized Boll's emphasis upon an 'embryonal mysticism' in place of a straightforward anatomic approach.

Embroynic rests.—The idea of an undifferentiated germinal layer as a source of cancer was first suggested during the blastema era; thus, J. Müller (1838 [280]) postulated an anomalous germ cell (semínus morbi) as the root of carcinoma. A succeeding generation of anatomists (e.g., Péréweserff, 1874 [303]), under Virchow's influence, continued to stress the plastic, embryonal character of the connective tissue stratum as the seat of neoplastic growth. This view also became a prominent feature of theories such as Boll's.

One of the first investigators to rework this idea into a major hypothesis was the Breslau pathologist Julius Cohnheim. Cohnheim argued that some defect or irregularity originating in the embryonal anlage became the focal point of tumor formation. His observation (1875 [82]) of a congenital striated muscle sarcoma of the kidneys—a myosarcoma striocellularis, grouped by Virchow among the teratomas—led him to assume that the tumor grew out of muscle germ cells separated from the renal primordia. Subsequently, he framed this view into a theory (1880 [83, pp. 634–654]) which widely influenced the contemporary outlook on tumor genesis. Cohnheim's theory specified that an overproduction of cells frequently occurred in organ morphogenesis. An excess of cells detached some time between differentiation of the germinal layers and completion of the organ primordia was capable of emerging as a new growth by virtue of the embryonal capacity for proliferation or bioplastic energy within these cells.

Cohnheim's theory of atypical tissue formation from the embryonal anlage, or embryonic rest hypothesis, was generally favored by the weight of strong clinical evidence. The numerous occurrences of congenital and early postnatal tumors had long been recognized. For example, malignancies stemming from both local malformations such as nevi and warts, as well as from more generalized organic irregularities appeared to be attributable to this cause. Newer additions to knowledge of a hereditary predisposition toward cancer (475, 1: 357–361) also confirmed, though more indirectly, to Cohnheim's explanation. A more decisive argument was that tumor cells commonly gave the appearances of undifferentiated embryonal types. Furthermore, the apparently accelerated proliferative behavior of artificially implanted embryonal tissues (405, p. 14) suggested that every tumor had a similar foundation. The theory was compatible with the embolus idea of metastases; Cohnheim (1877 [84]) gathered experimental evidence to show that detached, growing tissues distributed through the vascular transport became the foci of new growths at distant sites. (In 1896 Pianese (308) urged recognition as a co-founder of the theory of embryonic rests for the surgeon F. Durante on the basis of the latter's research on the structure of birthmarks. This work was allegedly reported a year before Cohnheim's 1875 publication (82). Durante (1894 [119]), about 1872, observed the rapid eruption of two sarcomas from dermoidal nevi submitted to surgical treat-

18 Nineteenth century research in this field is too extensive to be considered here. It is fully covered by Wolff (475, 1: 333–368) who discusses various phases of the teratoma problem with reference to Cohnheim's theory.
The assumption that these structures possessed a latent capacity for malignant tumor production led him to investigate the histogenesis of nevoid neoplasms. The following is an excerpt from Durante's conclusions as translated from the Italian (119, p. 35): "This research permitted me to firmly assume that malignant tumors were generated in the species of birthmarks which possess congenital connective and epithelial tissue elements. I presented my thoughts upon my embryologic and teratologic studies, as well as my observations upon the developmental and anatomico-pathologic course of several organs at the period of puberty, and all other relevant questions, in a small memoir on the structure of birthmarks published on the 26th of May 1874 in Palasciano's Archives, in which I arrived at the following conclusion: 'Elements which have retained their anatomic embryonal characters in the adult organism, or have regained them through some chemico-physiologic deviation, represent, in my opinion, the generative elements of every tumor variety and specifically those of a malignant nature. Such elements may remain enclosed within matured tissues for many years, giving no indication of their presence, until an irritation—a simple stimulus suffices—rekindles their vital cellular activities just as heat initiates activity within elements of the germinal macule of fowl's eggs. . . . In fact, if we briefly consider just how complicated are the disposition of tissues which concur in the organic composition of an epithelial cancer, we must at least admit that the genesis of cancer, at some determined point in the organism, derives from a reproduction of internal embryonal activities incorporated in the cell which possesses the requisite anatomico-physiologic apparatus necessary to their manifestation.'

An objection to Cohnheim's hypothesis was raised by Samuel (1879 [367]), and later by Hauser (1890 [178]), each of whom pointed out that it did not relate well to the formation of carcinoma from the standpoint of the epithelial theory. Virchow (1880 [433, pp. 189–190]) argued that the occurrences of certain tumors, such as neuromas at amputation sites, appeared to fall beyond the scope of the theory. Other gaps in the hypothesis also became apparent; e.g., isolated tissue-rests or superfluous embryonal masses did not invariably give way to neoplastic growth, nor was there any apparent reason why they should. Cohnheim's theory laid heavy emphasis upon the ready tendency for proliferation in embryonal elements. Nevertheless, the influence channeling this tendency into either the normal or neoplastic route still remained unexplained.

Cohnheim himself did not specify exact circumstances leading to disordered growth in embryonic rests; the role of certain indirect influences such as vascular complications and inflammatory hyperemia seemed to be implicated. The idea of gross mechanical insult as a prime cause of new growth was in its infancy when Cohnheim first expounded it in his 1894 article published in the Archiv für Dermatologie und Syphilis ([336], p. 189). It was later modified in 1899 when Cohnheim himself pointed out that it could not explain all instances of neoplasms. Cohnheim's theory laid heavy emphasis upon the ready tendency for proliferation in embryonal elements. Nevertheless, the influence channeling this tendency into either the normal or neoplastic route still remained unexplained.

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of the cellular complexes. (c) The concomitant occurrence of cellular dedifferentiation enhanced the capacity of the cellular complexes to more vigorously penetrate neighboring tissues. Embryonal tissues were most disposed to renewed multiplication by virtue of a lack rather than a loss of differentiation.

Ribbert’s emphasis upon the joint role of the connective tissue in the tumor process was ostensibly a retrograde step in the view of Gustav Hauser, (1890 [178]) and also in the opinion of Borst, although the latter (58, p. 686) praised Ribbert’s analysis of the transformation from normal to abnormal epithelium as well as his generally balanced perspective on the behavior of the epithelium in cancer formation; however, he could not entirely subscribe to Ribbert’s view of a concurrent hyperplastic modification of the connective tissue even though inflammation of the subepithelial regions in cancer might in fact indirectly stimulate the pathologic production of epithelium. Hauser was more emphatic in his insistence that the initiative in the neo-plastic process lay exclusively with the cell.

In a series of articles (179—182) Hauser contended that connective tissue alterations were entirely incidental to the performances of the epithelium in the development of carcinoma. These performances—here Hauser cited the results of his own investigations—were evidenced through an ever-widening zone of glandular degeneration proceeding into the underlying tissues. (This claim stood in contrast to Ribbert’s conclusion that the progress of cancer must be defined essentially in terms of constitutive rather than degenerative events.) According to Hauser, cancerous degeneration was associable with a biologic disordering of the epithelium, in which the cells appeared to undergo a loss of normal physiologic function by virtue of derangement of the cellular and nuclear dimensions, chromatin content, mitotic behavior, and protoplasmic character. These changes also appeared to be correlative to the tremendous proliferative tendencies in disordered epithelium and pointed to the conclusion that neoplastic cells represented a new biologic species.

**Anaplasia.**—A chronicle of late nineteenth century developments in cellular biology is beyond the scope of this report; however, it should be mentioned that by 1895 much fundamental knowledge on the vital processes of the cell under normal and pathologic circumstances had been laid down (473). Hauser’s attitudes are consonant with the new research perspective on the functional character of the cancer cell. This outlook has already been previewed in reference to Bard’s suggestion (1885) that the neoplastic cell existed as an atavistic type demonstrating reproductive deviations. Bard, in support of his premise, also pointed to the bizarre cytologic appearances of the neoplastic varieties.

The cytology of cancer was given special consideration by the peripatetic pathologist Edwin Klebs (1889 [211, p. 524]; 1890 [212]) whose theory of cancer formation as a conjunction of epithelial cells and leukocytes largely grew out of the assumption that the neoplastic cell demonstrated a characteristically atypical (asymmetric) mitotic behavior in which fragments of leukocytes participated. (The question of pathologic mitosis already had become a lively research issue (Arnold, 1879—1884 [14—17]), Alberts, 1890 [6], Schleich, 1891 [378], Ribbert, 1891 [333], Noeggerath, 1892 [292].) Hansemann (1890 [170]) emphasized that each asymmetric karyokinesis, resulting in the formation of disproportionate daughter cells, signified an altered state of cellular differentiation which conferred upon their progeny growth potentials differing from cells following a regular mitotic course. Subsequently (1891 [171]), this investigator correlated his conclusion with other cytologic data such as his separation among cancer cells having an abnormally poor chromatin complement (hypochromatism) and other atypical cell formations having an excessive chromatin complement (hyperchromatism).

These results which comprised the factual essentials of Hansemann’s theory of anaplasia (1893 [172]) provided, according to the author’s own specification, only a partial answer to the etiology of cancer. First, anaplasia merely represented a relatively abnormal situation; cells tended to become more anaplastic with respect to their degree of functional isolation from parent tissues. Secondly, in contrast to embryonal rests, the loss of cellular differentiation in anaplasia might hypothetically arise within them a capacity to express biologic tendencies culminating in growth deviations. Thirdly, the anaplastic cell would theoretically require an incitatory influence acting upon it in order to alter into a neoplastic cell.

Hansemann’s claims were met with countercharges such as that posed by Ribbert (1897 [343, pp. 32—36]) that the theory of anaplasia overlooked the hereditary growth controls built into cells at the inception of the organism. This rendered unlikely the radical alterations of cells or their descendents specified among the conditions of the theory. Hansemann’s hypothesis was also weakened by a variety of exceptions. For example, Stroebel (1892—1893 [394, 395]), Vitalis Müller (1892 [282]), Karg (1892 [214]), and others argued that asymmetric mitoses could not be correlated with a specific pathologic circumstance since they were to be found not only in cancer tissues but also in sarcomatous and benign growths, as well as in regenerating and other normal tissues in which prolific mitotic activity occurred. By 1900 more critical opposition to the theory was spearheaded by investigators such as Rudolph Beneke (1900—1901 [37, 38]) who began to stress the possibility of less apparent, but more fundamental functional reversions (kataplasia) which prompted disordered cellular growth.

**CONCLUSIONS**

A recapitulation of the principal topics discussed in this review is as follows.

**Tumor Morphology**

A settlement of problems relating to the pathologic anatomy of neoplastic diseases emerged as the crucial research issue in cancer at the turn of the nineteenth century. Solutions were attempted through various contemporary aspects of medicine; i.e., through a well-established surgical tradition in the British Isles, and through newly organized clinical centers in France and later in Germany, Switzerland, and Austria. An early approach to the structural pathology of tumors proceeded from the infant science of histology; investigators began to think of cancer and related diseases as de novo tissue productions.
A newly ascendant constitutional theory of cancer, with its pronounced emphasis upon empirical criteria, now came into vogue. Nevertheless, a concomitant advance in the competing localistic doctrine bore more promising consequences (a) as an experiential background for tumor transplantation research, (b) as the modern beginnings of the theory of metastases, specifically in the quarter century from Récamier (1829) to von Helmsbach-Meckel who recognized (1856 [267, pp. 62, 103]) the backward transport of cancer through the lymphatics, and (c) by virtue of improved clinical conceptions of tumor induction through environmental stimuli.

CELL BIOLOGY

The study of cancer was carried to the cellular level through the availability of achromatic lenses for microscopes, particularly after 1830. This technical innovation, despite its incipient deficiencies, ultimately secured a permanent taxonomic edifice for oncology on two fronts: (a) microscopic diagnoses of tumors at various sites provided the clinician with exact histologic data incorporating a variety of biologic details (e.g., the nature of secretory changes); by 1880 the diagnostician was working successfully with precise categories of neoplasms; (b) through microscopic and other newly devised laboratory techniques, the pathologist simultaneously settled many pathogenic questions in oncology. This research assessed both the structural and functional sources of tumor materials through a succession of growth concepts which eventually focused investigative thought upon the behavioral peculiarities of the neoplastic cell itself. By 1900 it became possible to think of cancer and other autonomous new growths as submicroscopically defective cellular species.

INHERENT SUSCEPTIBILITY

Hereditary aberrations and physical and chemical disturbances within the tissue environment as internal seats of disordered growth, became pivotal issues in oncology after 1850; the static dyscrastic viewpoint, in consequence, took on the more meaningful aspects of a search for physiologic irregularities in cancer (Broca, 1852 [63]). In later years this evidence combined with other features of the constitutional character was summoned as direct proof for the existence of intrinsic, predisposing causes of neoplastic diseases. Cohnheim’s hypothesis, supported by a broad spectrum of anatomic knowledge, emerged as the highpoint of this approach though it failed as an all-embracing etiologic argument. However, this and other theories in the same genre allowed for the coincidence of extrinsic influences in tumor genesis; they thereby constituted sufficiently enlarged platforms for subsequent experimental efforts.

ENVIRONMENTAL CARCINOGENESIS

Interest in the carcinogenic potential of environmental constituents grew into a strong current of activity in mid-nineteenth century cancer research programs. Perceptive clinical judgments underlay the early advance of this field; for example, Sir Astley Cooper (1830 [86, p. 226]), a significant contributor to the diagnosis and surgical treatment of chimney-sweeps cancer, was among the more influential workers who expressed the common medical consensus that this disease was to be ranked in the category of an occupational hazard. Many investigators (cited by Lortet, 1861 [242, p. 47]) also took into account the influences of climate and geographic location, among other factors, in their evaluations of the neoplastic processes. By virtue of these observations the critical role of external functional stimuli became the mainspring of many theoretical approaches to tumor induction. These aspects lent weight to the rapidly ascendant research conviction that cancer and related diseases presented medical science with a many-faceted problem.

RESEARCH ON HUMAN CANCER AND EXPERIMENTAL TUMOR PATHOLOGY

The principal research advances discussed in this report are the results of gross and microscopic diagnoses of human cancers, which made possible a sound edifice of knowledge for the prosecution of experimental pathologic. Thus, the experimental trials by Peyrilhe and his contemporaries predated by more than a century the opening of the first fruitful moves in the area of tumor transplantation research. “At a time when the test of direct experiment is being applied for the elucidation of many of the complex problems of animal life and its modification by disease,” according to one prominent pathologist of the era (1883 [128, p. 241]), “it would be surprising if the mystery of tumour formation had not been attacked from the same direction.”

As an incipient discipline before 1900, experimental oncology added suggestive rather than conclusive details to the research picture. For example, the early record of implantation research in the nineteenth century led to a rapid awareness of the need for studying growth under standardized conditions. Epidemiologic oncology was stimulated by the recurrent questions of infective and environmental influences in cancer. It is interesting to note in this connection that not only a ‘virus’ theory emerged from this background, but also a ‘tobacco’ hypothesis of carcinogenesis. Although each of these aspects began its experimental history in the new century (e.g., Rous, 1910; Yamagiwa and Ichikawa, 1915), each had significant precursors in the old century (e.g., see Wilhelm Müller, 1871 [280]; Power, 1893 [315]).

Cancer research thus represents a slowly unfolding episode in which the past and present are but sequential scenes.

ADDENDUM

over, space limitations have made it necessary to deemphasize
the numerous auxiliary procedures involved in histologic tech-
niques of biopsy and the specimen preparation.

Simultaneous progress in veterinary pathology (see Stricker's review of animal cancers in Arch. klin. Chir., 65: 516—526, 1902) is an important collateral area of development.

Occupational and other facets of environmental carcinogenesis are superficially treated. A comprehensive monograph on this subject would be a valuable addition to the historical literature on cancer. The complexities of environment, occupation, and cancer require special considerations in historical development. Pending the availability of such a history, the reader is referred to historical data included in reviews of recent research in carcinogenesis and epidemiologic oncology, e.g., P. R. Peaceoek (Cancer, R. W. Raven, editor, Butterworth: London, 1979—80, Vol. 1: 32—75) and W. C. Hupeuer (Ibid., pp. 404—406).

Various readers may note the omission of American contributions in this review. There was little justification for an 'American School' since nineteenth century American investigators were, for the most part, apprentices in the laboratories of the European masters. Carmalt, Hoeber, and Wadsworth, mentioned in the discussion, are examples. John Collins Warren (Boston), a pupil of Sir Astley Cooper and Dupuytren, was the first American to write a treatise on tumors (Surgical Observations on Tumours with Cases and Operations, London: Churchill, 1839); its influence on European authors such as Walter Hayle Walshe is discussed by Pollay (313). The universality of scientific interests which characterizes Johannes Muller and Virchow also distin-
guishes the career of the anatomist Joseph Leidy (Philadelphia). Leidy (Proc. Acad. Nat. Sci., Philadelphia, 5: 201—212, 1851—1852), implanted fragments of human (mammary) cancer beneath the integument in a frog. After 5 months Leidy noted that the fragments formed vascular connections with the integument and to each other. The experiment was repeated with similar results, from which Leidy concluded that cancer was inoculable. "for, as in the experiments, the cancerous fragments continued to live when introduced into cold-blooded animals, they would probably not only continue to live when introduced into warm-blooded animals, but would grow or increase in size" (p. 212). Leidy perhaps was considered the Feyrile of America.

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