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# Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s

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BERCHTOLD, N. C., AND C. W. COTMAN. *Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s.* NEUROBIOL AGING **19**(3) 173–189, 1998.—Most histories of senile dementia commence with Alois Alzheimer's description in 1906 of the first case of Alzheimer's disease, yet the history of senile dementia before 1906 is quite rich, dating back to the ancient Greek and Roman philosophers and physicians. Over the 2500 years since ancient times, the concept of senile dementia has evolved from a rather vague notion that mental decline occurred inevitably in old age, to become defined today by a distinct set of clinical and pathological features with the potential for treatment and prevention within grasp. Throughout history, many elderly individuals with unpredictable behavior were sequestered in institutions, and the line between mental disorders and senile dementia was hazy at best. The identification of Alzheimer's disease at the onset of the 20th century was a turning point for the understanding of senile dementia, and the concepts and histological findings presented by the early researchers of Alzheimer's disease remain relevant still today. Indeed, these early findings are proving to be a continuing source of insight, as many of the issues debated at the turn of the century remain unresolved still today. This paper thus traces the history of the evolution of our current conceptualization of Alzheimer's disease from the amorphous Greco-Roman concept of age-associated dementia. © 1998 Elsevier Science Inc.

Dementia Senile dementia Alzheimer's disease History Greco-Roman Aristotle Galen Medieval Esquirol Psychiatry Perusini Fischer Kraepelin Fischer Senile plaques Neurofibrillary tangles Neuropathology

## GRECO-ROMAN PERIOD

Upon examining translations of exerpts from various ancient texts, it becomes readily apparent that the condition of cognitive decline in aged individuals has long been a recognized affliction. One of the earliest references to age-related mental deficiency is attributed to Pythagoras, the Greek physician of the 7th century B.C. Pythagoras divided the life cycle into five distinct stages, commencing respectively at ages 7, 21, 49, 63, and 81, the last two of which were designated the senium, or "old age"—a period of decline and decay of the human body and regression of mental capacities (55). He commented on this late stage of life where "The scene of mortal existence closes, after a great length of time, to which, very fortunately, few of the human species arrives. The system returns to the imbecility of the first epoch of the infancy" (65, pp.129–130). Such extreme regression in mental capacities with age must have been fairly frequently observed, or at least must not have been considered an oddity, because it was taken seriously enough to be incorporated into lawmaking. Solon [500 B.C], a Greek judge, took senile cognitive decline into consideration when he was revising the laws regarding the making of wills (senile—denoting "aged," derived from senium). Solon amended the laws of the time that dictated that an inheritance was to be divided among the family, and annexed the legality of including an extra-familial heir, "provided judgment was not impaired by pain, violence, drugs, old age, or the persuasion of a woman" (152).

It is unclear to what degree Hippocrates [ca. 460–377 B.C.], who is considered the Father of Medicine, reflected upon age-related mental decline. According to one source (55), Hippocrates included the term "paranoia" in his classification of mental diseases, where "paranoia" (used synonymously for Pythagoras' "imbecility") represented the deterioration of mental faculties in the state of old age. Halpert (55) indicates that "paranoia" was believed by Hippocrates to have an organic etiology and a fatal prognosis, but it is not certain whether Hippocratic writing actually was this explicit regarding the condition of "paranoia," or whether the source interpreted this from Hippocratic theory which ascribed all illness to an imbalance in the four cardinal body fluids (blood, phlegm, yellow bile, and black bile) (96,159). If this interpretation

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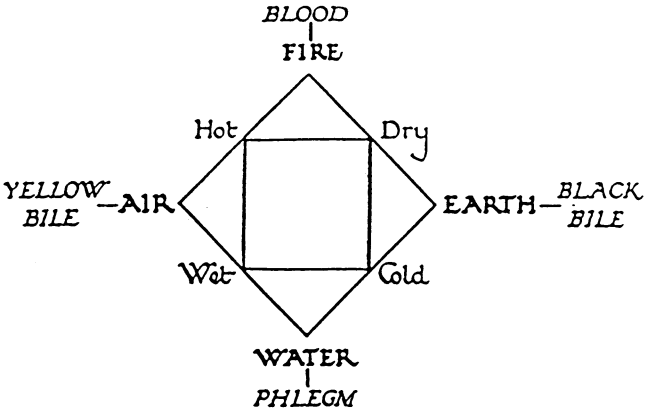


FIG. 1. The ancient Greeks held that there were four cardinal body fluids (or "humours"), and four primary and opposite fundamental qualities (hot, cold, wet, dry). Each humour was correlated with a particular mental state or temperament (blood, sanguine; black bile, melancholy; phlegm, phlegmatic; and yellow bile, choleric). Illness, such as mental disturbance, was thought to result from an imbalance in the systems of humours and qualities. In addition, the four stages of life were characterized by changes in the balance of the humours and qualities; aging, for example, rendered the body "cold and dry." Parallels were drawn between the four humours, and the four Elements (earth, air, fire, water), which composed all Matter. This theory explaining sickness remained popular through the 18th century (see also Fig. 4). Figure printed from (144) by permission of Oxford University Press.

of Hippocrates' writings is accurate, it would indicate a markedly early attempt to explain age-related mental dysfunction as stemming from an underlying organic etiology. On the other hand, another source (153), claims that "although incompetent behavior was recognized in the elderly Hippocrates did not include it among his mental disorders" (p. 23), and interprets this to indicate that such cognitive deterioration was likely to be considered merely a routine part of the aging process. The two interpretations are in fact not mutually exclusive. It is most likely that Hippocrates was indeed aware of mental decline in the elderly, and that he did not consider it an abnormality, but rather, an unfortunate and inevitable consequence of aging, because aging itself was accompanied by changes in the balance of body liquids that rendered the body "cold" and "dry" (55) (see Fig. 1).

Plato and his student Aristotle [384–322 B.C.] both comment in their writings on mental failure in old age, with the conviction that old age is inseparable from mental failure. This can be interpreted from Aristotle's statement that old people are useless for high administrative posts because

> there is not much left of the acumen of the mind which helped them in their youth, nor of the faculties which served the intellect, and which some call judgment, imagination, power of reasoning and memory. They see them gradually blunted by deterioration and see that they can hardly fulfill their function. (55, p. 422)

Aristotle's writings do not mention the possibility of any exception to mental decline in old age, and thus he probably was of the view that dementia with the onset of advancing age was inevitable, just as the passage of time is inevitable (55). Accepting the inexorability of this affliction, Aristotle did not seek to attribute this mental change to any underlying factor. In retrospect, it is likely that Aristotle actually hampered progress in identifying an underlying physiological source (i.e., the brain) for senile cognitive decline. Although he made important contributions, some of Aristotle's ideas concerning the functioning of the human body were quite erroneous, and had the result of misdirecting thought for several centuries. One such theory was his conviction that it was the heart which was the source of life and the seat of human intelligence. The brain—bloodless, cold, and without *sensation*—was meanwhile demoted to a "steaming gland there to cool the heart" (159). This is unfortunate, for as an exemplary doctor, scientist, and philosopher, Aristotle came to be one of the most widely respected of the ancient authorities, and his teachings were rarely questioned. His views on the heart and brain effectively reversed the growing awareness of physicians that the brain was the central organ which controlled the functions of all others and was also the seat of the mental faculties, a theory originally put forward in the 6th century B.C., by the Greek physician and anatomist Alcmaeon, and which was endorsed by Hippocrates (159).

While Pythagoras, Hippocrates, Plato, and Aristotle seemed to view mental deterioration as inevitable in old age, the Roman philosopher Cicero [2nd century B.C.] was perspicacious in observing that "senile debility {sic esta senilis stultitia}, usually called dotage, madness or delirium {quae deliratio appelair solet}, is a characteristic, not of all old men, but only those who are weak in will {senium levium est}" (55, p. 422). Cicero further suggested that an active mental life could prevent or at least postpone mental failure (85), a theme which is still well alive with us today (18,64,137). Cicero insisted that

> it is our duty to resist old age; to compensate for its defects by a watchful care; to fight against it as we would fight against disease. . . . Much greater care is due to the mind and soul; for they, too, like lamps, grow dim with time, unless we keep them supplied with oil. . . . Intellectual activity gives buoyancy to the mind. . . . Old men retain their mental faculties, provided their interest and application continue. . . . (85, p. 2)

Cicero's influence on the medical milieu was undoubtedly overpowered by Aristotelian thought, and his remarkably perceptive views, that dementia was not an inevitable consequence of aging and that it could be offset by keeping the brain active, did not take root.

While the likes of Pythagoras, Hippocrates, Plato, Aristotle, and Cicero commented on the weakening of mental capacities seen with advanced age, it is likely that they represented an elite minority and that the condition of age-related mental decline was not a common topic of medical and lay discussion. The medical compilations of the encyclopedist Aurelius Celsus, in his work *De Re Medicina* [30 A.D.], do not mention mental impairment in old age. While he does mention paralysis with old age, there is no mention of old age under the section on insanity—insanity referring to any incomprehensible mental condition including dementia (85). However, it is not clear how representative his work actually was of the views of his contemporaries, because Celsus himself was not a physician, and his work is considered essentially a compilation based on the Hippocratic Writings (84,117).

The Roman physician Galen [150–200 A.D.] was a major figure in the history of medicine whose work was not only highly recognized but indeed became part of the medical scriptures for at least the next 1000 years. Galen systematized the Greco-Roman medical knowledge of the ancient authorities, with an emphasis on Hippocratic as opposed to Aristotelian views on the brain's importance, and additionally left voluminous writings on all the major medical, scientific, philosophical, ethical, and religious issues of his time (84,96). In contrast to Celsus' encyclopedia, Galen included "morosis" (his term for dementia) in his list of mental diseases, and listed old age as one of the situations in which it occurred. Those afflicted with morosis were described by Galen as "some in whom the knowledge of letters and other arts are

totally obliterated; indeed they can't even remember their own names. . . . Even now it is seen, that on account of extreme debility in old age, some are afflicted with similar symptoms" (153, p. 24). In addition, the writing of Galen indicated that old age in itself had become viewed as a diseased state: "old age is not natural in the same way that feeding and growing are; the latter two can be considered as natural processes, while the former is not, being instead an inevitable infection of the body" (55, p. 422). With this pessimistic view of old age, it is no wonder that mental deterioration was seen as an inevitable condition of the senile period, which Galen, showing his Hippocratic roots, attributed to a "rarefaction and diminution in quantity of the animal spirits and from the coldness and humidity of the brain" (55, p. 422).

In short, through the works of such major historical figures as Pythagoras, Hippocrates, Plato, Aristotle, Cicero, and Galen, it is clear that age-related cognitive decline was recognized as early as the 7th century B.C., that in the Greco-Roman period mental deterioration was considered by most as an inevitable consequence of aging, and that aging itself had come to be considered a disease process. It is likely that the equating of old age with an inevitably demented state by the Greco-Romans laid the foundation for the changing definition of the term senile, from its original sense denoting "advanced age" to its later usage denoting "demented." The first steps toward classification of dementia were taken during the Greco-Roman period, with Galen identifying dementia in the senium as a mental disease. It must be kept in mind that the age-related dementia described by the Greco-Roman physicians and philosophers refers to a larger set of disorders than what would be referred to as senile dementia several centuries later. The Greco-Roman diagnosis of senile debility undoubtedly included dementia due to a number of causes, including central nervous system (CNS) infections, depression, vitamin deficiency, cerebral infarcts, among others, in addition to the disorder that is identified in the 20th century as senile dementia of the Alzheimer's type (hereafter in the text, "senile dementia" refers to cognitive decline that is not attributable to any cause other than aging, due to the limitations of diagnosis and medical knowledge of the respective periods throughout history. The meaning of the term "senile dementia" thus will change throughout the centuries as increasing differential diagnostic capability is achieved). Further evolutions of thought that emerged from this Greco-Roman period include a shifting emphasis from the brain to the heart as the source of mental processes, and those who favored the brain would remain a minority for the next millennium.

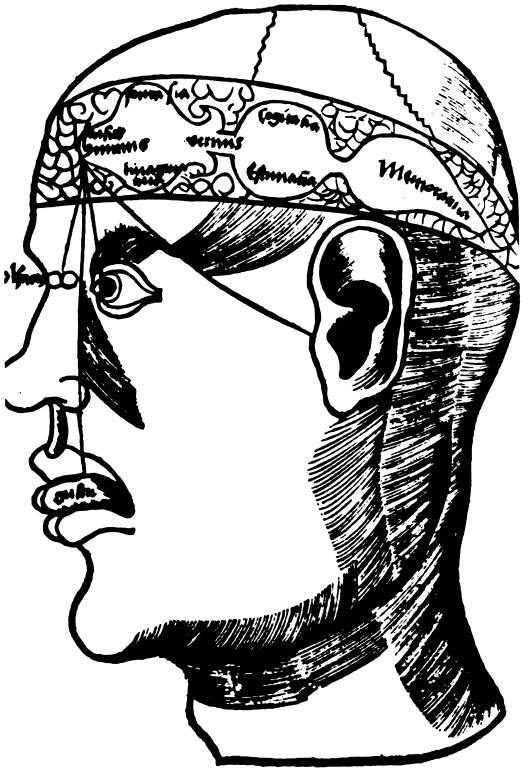

FIG. 2. The "ventricular system" portraying the medieval concept of physiological psychology, commented on by Roger Bacon. Memory is stored in the posterior ventricle, thought and judgment arose from the middle ventricle, and imagination originated in the anterior ventricle. The reference to the brain as the source of mental processes is noteworthy, because for the prior millennium, and for centuries following the medieval period, the heart had predominated as the seat of human intelligence. Woodcut by Reisch, in 1512.

## MEDIEVAL INTERLUDE

Commentary on the topic of senile cognitive decline seems to have dwindled to nonexistence during the period after Galen, until well into the 16th century (55,85,153). This trend parallels the stagnation which afflicted all scientific, anatomical, and physiological research following Galen's death, and the onset of the decline of the Roman Empire. (This reflects only the state of affairs in what today is considered the Western world. The Middle East and Far East in contrast, experienced several centuries of flourishing scientific and technical progress. For the sake of space, contributions from the Middle East and Far East have been omitted. An overview of general scientific progress in both East and West can be found in Bernal's *The Emergence of Science* (10).) Not immune to the corruption, chaos, and general upheaval that accompanied the decline and fall of the Roman Empire, the status of doctors and medicine declined drastically during this period. The Church arose as a powerful force and came to dominate all aspects of life, and it was the clergy who had the monopoly on knowledge and education. With the word of the Ancients taken as unquestionable authority, theological doctrines and dogmas prohibiting any heretical learning through observation and research, and the religious beliefs of this time holding that disease was a punishment for sin, it is little wonder that little, if any, progress or insight was achieved in the medical arena (159).

One of the few references to senile dementia that can be found from this period comes from the Franciscan friar Roger Bacon [1214–1294]. This individual, who was irresistibly drawn toward natural science and experimental research, was a rare exception to his time, because the Church disapproved highly of empiricism, regarding it as clearly unnecessary to salvation. In addition, the dependence of observation on the senses was seen to depreciate the value of revelation, and thus was construed as heretical (10). In spite of the views of the Church, Bacon made prolific and astute observations and inventions (117,153). For his brilliance, he was imprisoned, and saved from immediate execution only by his ties to influential friends in the Church. During his solitary confinement, a few years before his death at age 80, he wrote the work *Methods of Preventing the Appearance of Senility*, in which he commented that "in the posterior part [of the brain] occurs oblivion and memory concerning which Haly Regalis speaks in his first theoretical tratise, saying that old age is the home of forgetfulness" and that "An injury to the reasoning faculty happens in the middle part of the brain. . . . An injury to the imagination occurs in the anterior part of the brain" (153, p. 25) (see Fig. 2).

This work was based largely on the theories of the Arabian

Galenists, and the familiar theme of the inevitability of mental decline in old age is reiterated (153). Quite remarkable, though, is the reference to the brain as the source of memory and thought processes, because for the prior millennium and for the next several centuries, the heart dominated as the seat of the soul and mental processes. Bacon was inarguably a light in a sea of darkness, and it would be several centuries before tangible progress would be made in any medical field, let alone a subject as resignedly accepted as senile dementia.

## TO THE NINETEENTH CENTURY

Very little progress regarding the subject of dementia developing in the senium was made until essentially the 19th century, because dementia continued to be viewed as an inevitable feature of aging (55,85,153). However, it is clear that by this time age-related cognitive decline was a recognized and undoubtedly common feature of life. Awareness of senile dementia was not restricted to the medical community, as this subject made frequent appearances even in literary descriptions. Chaucer [ca. 1343–1400] commented on the inevitability of dementia: "with old folk, save dotage, is namore" (153), and Shakespeare [1564–1616] made numerous keen descriptions of dementia through his characters in several plays, most famously in *Hamlet* and *King Lear* (140). Shakespeare may have been more medically astute than medical writers of the time, as he not only took note of age-related cognitive decline, but also made clear distinctions between senile decay and "plain madness," and commented on both the cognitive and the affective changes that accompany senile dementia (85). Other than these literary references, there are few outstanding references to age-related cognitive decline deriving from this time period, as little medical attention seems to have been paid to the inevitable senile dementia. There was, however, an upwelling of interest in other dementias, which may be related to the rampant persecution of witches during the 1400–1600s. Victims of the witch trials undoubtedly included individuals with cognitive disorders, and their persecution would have brought attention to such disorders (55,85,96) (see Fig. 3). It is useful, for the purpose of tracing the changing conceptualization of senile dementia, to consider the evolution in the conceptualization of other cognitive disorders, because advances in these fields contributed to the establishment of age-related cognitive decline as a unique entity distinguished from other dementias and, in addition, provided later impetus to reevaluate ideas concerning senility.

Starting in the 16th century, there was an increasing preoccupation in the medical community with discussion of mental sickness. A widely read textbook on medicine by Barrough, published in 1583, laid out the main divisions of the recognized cognitive (mental and neurological) disorders known at that time, based on Galen's classification. Distinctions were made between frenesy (fever induced delirium), mania (no fever, plain madness), lethargy, melancholie, coma, congelation (catatonia), apoplexy (paralysis), epilepsy, and memory loss (6). Under the heading of memory loss, there is a distinction between memory loss and loss of reason, and Barrough suggests a different disease basis depending on whether only one or both faculties are lost

> the losse of memoire chaunceth sometime alone, and sometimes reason is hurte with it. It is caused in the lethargie and other soporiferous diseases. . . . If reason be lost together with the memorie, then the affect is called Fatuitas or stultitia, [that is] foolishnes or doltishnes, and both these do come of one disposition, but that is more vehement wher both are hurte. (6, p. 25)

As far as underlying causes for these dementias were concerned, there was little knowledge on which to base a diagnosis, and the presence or absence of fever based on the rate of the pulse was the principal diagnostic guide (62). Showing his Galenist and Hippocratic roots, Barrough (6) emphasized abnormalities in the brain as the source of these disturbances, for example frenesie is "an inflammacion of the filmes of the braine with an acute fever, causing raging and vexation of the mind" (p. 25), and apoplexy is a "stopping of the brain" (p. 26). Not only did Barrough ascribe mental derangement to the brain, he further proposed an explanation of the source of the problem in the brain, based on Hippocratic views of disease stemming from imbalances in mixtures of body liquids with a resultant offsetting of the proper mixture of temperature and dampness. For example, lethargie was "caused of fleume, which cooleth the braine overmuch, and moisteneth it, and thereby provoketh sleep" and with "overmuch cooling you may turn the frenezy into a litargy" (p. 25) (see Fig. 4).

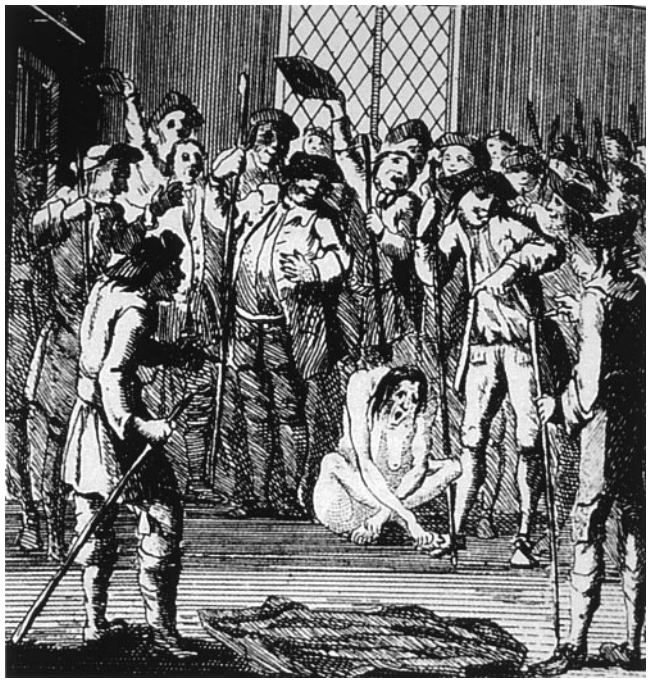

FIG. 3. Victims of the witch trials undoubtedly included many individuals with cognitive disorders, and it has been speculated that some victims were likely to be elderly individuals afflicted with senile dementia, such as may be the case for this unfortunate case from Tring in Hertfordshire. Woodcut located in the Wellcome Institute Library, London.

In the 17th century, the different branches of dementia became better characterized behaviorally and were shaped into more defined and distinct concepts. In addition, as dissection of the human body became tolerated, there was an increasing trend toward searching for underlying physiological changes in the brain that might be the source of mental disorders (117,153). Thomas Willis [1621–1675], an avid anatomist and the personal physician to King Charles II, offered a precise classification of dementias in 1684 in a chapter of his *Practice of Physick* (165). Willis identified, with admirable accuracy and insight, causes for dementia, based on his clinical and anatomical knowledge. He recognized that "Stupidity or morosis or foolishness. . . signifies a defect of the intellect and judgment, yet it is not improperly reckoned among the Diseases of the head or brain" (11, p. 831), and attributed "foolishness" to the following causes, among others: 1) congenital factors, 2) age ("some at first crafty and ingenious become by degrees dull, and at length foolish by the mere declining of age"), 3) head injury ("great strokes or bruising of the head specially such

FIG. 4. The four temperaments, from the *Guild Book of the Barber-Surgeons of York.* The drawing, from the 1500s, illustrates both the ages and mental states which were associated with each humour (see also Fig. 1). The phlegmatic humour, denoting apathy or sluggishness, is associated with old age. Top left, melancholic; top right, sanguine; bottom left, choleric; bottom right, phlegmatic. Printed by permission of The British Library (R97/1263).

as happen from a fall from high place"), 4) alcohol and drug abuse, 5) disease ("it is observed that some men have contracted also foolishness by reasons of cruel diseases of the head"), and 6) prolonged epilepsy (11, p. 831). Other anatomists attempted to find precise correlates for mental disorders in the brain's gross anatomy or morphology. Unfortunately, as Torack (153) points out, the majority of mental disorders do not have an evident anatomical correlate. As a result, most of these descriptions of the physiology of the demented brain are less than objective, and serve primarily to illustrate the unshakable faith in Galen's "scriptures" that prevailed. For example, "old" meant cold and dry to Galen, so accordingly must the brain appear in advanced age, and with mental failing. Indeed, the following quotes (153, p. 25) illustrate this adherence to Galen's views regarding the aged brain, as many respected authorities observed that in the elderly or demented "the brain is seen to be pressed by an excess of humidity or cold, the texture of the brain being too solid and crumbling" (Bonet, 1679), "the brains of the elderly upon examination with a knife are more hard" (Boerhaave, 1700), and "in madness the brain is dry, hard and friable" (Haller, 1763). The anatomist Morgagni, however, renowned for his structured and disciplined approach to empirical observation, did not allow his objectivity to be swayed, and commented in 1761: "I do not lay so much stress upon this hardness, I would have you know that in some persons whose minds had not been disordered, I did not find the cerebrum less hard" (153, p. 26). Matthew Baillie [1761–1823], an eminent English physician and author of a textbook on pathology, may have been the first to comment on cerebral atrophy in an aged demented individual: "the brain is sometimes found to be considerably firmer than in a healthy state. Under such circumstances, the ventricles are sometimes found enlarged in size and full of water" (153, p. 26), but he did not recognize this ventricular dilation as a sign of atrophy.

Toward the end of the 18th century, scrutiny of the brain and nervous system spread beyond anatomists to the realm of pathologists. One such pathologist was William Cullen, whose pathogenic concept held that the point of origin of all illness was the nervous system (62,115). Following the lead of Willis and others, Cullen felt that the old pathological theories, which were based on Aristotle's "circulation of the blood" theory and on Hippocratic theory on the "nature of the humours," needed to be replaced by a more modern theory, based on disturbed nervous function. In the year 1776, without much knowledge of the etiology of disease at his disposal, he proceeded to reclassify all diseases into four classes, one of which was entitled Neuroses (nervous diseases). It is in Cullen's classification, under Neuroses, that senile dementia is recognized for the first time as a medical entity, defined as "decay of perception and memory, in old age {Amentia senilis}" (34, p. 478).

Essentially, from the time of the ancient Greeks and Romans to the 19th century, no sweeping progress in the conceptualization of senile dementia had been made. The broad concept of dementia underwent some gradual refinement with the categorization of different conditions in which dementia is found, and the narrower concept of senile dementia (Amentia senilis) established itself as a medical entity. Abnormalities in the brain were suspected as the source of dementia or mental aberration, and anatomists scrutinized the brain's gross appearance (color, texture, size of pineal, appearance of meninges, blood vessels, color of fluid emanating from the tissue) in search of an anatomical correlate of dementia, but to little avail. Brain atrophy accompanying Amentia senilis was not yet remarked upon, possibly due to the heterogeneity of disorders which continued to be united in this medical entity.

## THE NINETEENTH CENTURY

Starting with the turn of the 19th century came a series of dramatic and invaluable developments that were pivotal to progress regarding all mental disorders, including senile dementia. The first major steps were the humanitarian reforms implemented by Phillippe Pinel [1745–1826], the famous French physician to the Bicêtre asylum, professor of pathology and hygiene, and consulting physician to Napoleon (62). Up until this time, mentally insane individuals, including senile (aged) dements, had been kept incarcerated in prisons and submitted to their ghastly conditions and treatment (96,153) (see Fig. 5). In his book entitled *Treatise on Insanity*, printed in 1806, Pinel condemned this system that routinely "abandoned the patient to his melancholy fate, as an untamable being, to be immured in solitary durance, loaded with chains, or otherwise treated with extreme severity, until the natural close of a life so wretched shall rescue him from misery" (112, p. 605). Despite facing much resistance and outrage from the public and government (many individuals were of the opinion that Pinel himself was mad and should be incarcerated), Pinel succeeded in establishing his view that madness was not a crime but a disease. As a result, the insane were unshackled, and institutions designed

FIG. 5. Phillippe Pinel at the famous Bicêtre asylum, implementing humanitarian treatment of the mentally insane. Given that even today, many of the behavioral disturbances associated with Alzheimer's disease show similarities to mental disturbances, it would be surprising, in retrospect, if some Alzheimer's disease cases were not included in the category of the institutionalized, as may be depicted in this painting by Charles Muller. Painting located in the Library of the Academy of Medicine, Paris, France.

for more humane and appropriate care were established (96). In addition to introducing a humanitarian attitude toward the mentally insane, Pinel as a physician attempted to change the "armchair theorizing" and speculation that constituted the customary approach to psychiatry, by applying scientific principles of objective observation to the clinical setting (62).

Pinel's humanitarian reforms made possible widespread clinical and pathological observations of mental disorders, and accordingly, there was a rapid increase in such observations (96). For these clinical analyses to be useful and understood in all circles, it was imperative that a systematic terminology be applied to the clinical observations, and additionally that there be an organized system of classification of the mental disorders. It was Pinel's favorite and most illustrious student Esquirol [1772–1840] who recognized this need to create order out of the existing chaos, and who proceeded to reassess and redefine old terms, create terms for new concepts, and give names to newly identified subtypes and categories of mental disorders (62,96). By introducing systematic clinical observation and exact description using precise terminology into psychiatry, Esquirol established the foundation of modern classification of mental disease (62).

In addition to these very broad and fundamental changes, Esquirol made specific refinements of the categories of dementia. One such refinement was that of making the fundamental distinction between "dementia" and "amentia," where dementia is "the loss of mental faculties consequent on disease, and 'Idiocy'. . . is not a disease, but a condition in which the intellectual faculties are never manifested; or have never developed sufficiently to enable the idiot to acquire . . . knowledge" (62, p. 732). Previously, in the mid-17th century, Willis had identified both old age and congenital factors as sources of dementia, but did not identify the dementias from the two sources as fundamentally different. Esquirol characterized the difference succinctly in one of his most widely quoted statements, that "A man in a state of dementia is deprived of advantages which he formerly enjoyed; he was a rich man who has become poor. The idiot, on the contrary, has always been in a state of want and misery" (62, p. 733). Furthermore, Esquirol described the stages of cognitive decline that very accurately reflected the progression of senile dementia (as conceptualized in the 20th century):

> senile dementia results from the progress of age. There is. . . loss of sensibility along with . . . the faculty of understanding, before reaching an extreme state of decrepitude. Senile dementia . . . commences with feebleness of memory, particularly recent memory; attention . . . becomes impossible; the will is uncertain, the movements are slow. . . . (85, p. 9)

After Pinel and Esquirol had laid the groundwork for the systematic observation and description of mental disorders, it became possible to recognize subtler characteristics of mental disorders that included dementia as one of their features, and to tease apart related groups of features from a general pool of mental dysfunction, in order to describe distinct disorders (96). As a result of differential diagnosis of other mental disorders, the concept of senile dementia began to emerge as a narrower and more defined condition. For example, in 1873–4, the condition of general paresis was established as a distinct category from senile dementia (85), and, in 1898, Kraepelin unified under the name of dementia praecox, the rather obscure and disparate characteristics of the disorder which we today call schizophrenia (85,96).

Paralleling the far reaching changes in *psychiatric* classification and clinical observation of mental disorders that commenced at the end of the 18th century and flourished in the 19th century, so did the end of the 19th century see the introduction of new concepts and techniques that would have equally dramatic implications, for the *etiological* characterization of mental disorders. Continuing the trend that began in earnest at the end of the 17th century, anatomists analyzed the brain's gross appearance for clues to brain abnormalities in mental disorders. By 1860, there was a general appreciation of the change in brain weight that accompanied some dementias, as well as aging. Morel, in his work *Traités des Maladies Mentales*, stated that

> comparison of brain weights in the various forms of insanity shows that the heavier weights are found in cases of recent onset. Chronic cases show more often a general impairment of intelligence {dementia}. Loss in brain weight—a constant feature of dementia—is also present in ageing, and is an expression of decadence in the human species. (12, p. 9)

Inexplicably, this decrease in brain weight was not recognized to be due to atrophy until 1864, when Wilks provided the first definitive description of atrophy: "Instead of the sulci meeting, they are widely separated and their intervals filled with serum and which, on being removed with the pia mater, the full depth of the sulci can be seen" (165). Wilks initially described this atrophy as being due to chronic alcoholism and CNS syphilis, and later extended the observation to be characteristic of senile dementia as well. Once atrophy had been so succinctly described, it became an easily identifiable feature, and henceforth became a constant feature in the pathology description of dementia (see Fig. 6).

As was the case for atrophy, many pathological features were first observed in brains from individuals afflicted with general paresis (due to CNS syphilitic infection) and were then subsequently investigated in relation to other dementias. It is estimated that general paresis accounted for at least 10% of dementias at that time (96). Thus as one of the most common and devastating forms of dementia, it generated much interest as to its etiology, and it became the first dementing disease to be clearly defined by psychiatrists. One pathological feature characteristic of syphilitic infection is a reduction in the diameter of blood vasculature, due to swelling and proliferation of endothelial cells (96). In addition to afflicting the peripheral vasculature, this pathology was visible in the cerebrovasculature, and as a result, attention was directed toward cerebrovascular changes as a contributing factor to onset of

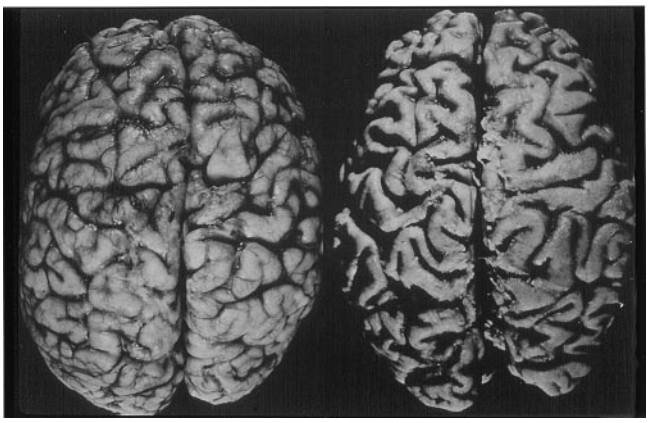

FIG. 6. The obvious atrophy of the brain, which is acknowledged today as a consistent feature of the senile dementia brain, was first recognized in the mid 1800s to accompany senile dementia. Here, this severe atrophy is apparent when comparing a senile dementia brain (right) with an age-matched control brain (left).

dementia. The cerebral atrophy that had previously been identified as consistently characteristic of many demented brains was soon correctly attributed to cell death due to focal lesions subsequent to strokes; the accompanying dementia was seen to be resulting from a gradual strangulation of the blood supply to the brain (153). Alois Alzheimer [1864–1915] and Otto Binswanger [1852–1929] both extensively described this arteriosclerotic brain atrophy in the 1890's (48,54,88,134,158). By this time, atheromatous degeneration of blood vessels with accompanying stroke had generally become accepted as a necessary precursory event for the development of senile brain atrophy and senile dementia (48). This was to remain the prevailing theory regarding the cause of senile dementia well into the 1960s.

At the same time that vascular disease was becoming established as a predominant cause of senile dementia, improvements in microscopy were being made and new histochemical techniques were being developed, which allowed elements of the nervous system to be visualized for the first time. These developments opened the door to a whole new world of pathological consideration of dementia, and henceforth new concepts regarding the etiology of dementias spilled forth at an unprecedented pace. In 1892, using the recently discovered carmine stain, Blocq and Marinesco described a novel pathological feature, the accumulation of an unidentified substance into plaques, in the brain of an elderly epileptic patient (20). In 1898, this same pathology—under the name of "miliary sclerosis"—was observed by Redlich in two cases of senile dementia (116). It was Fischer, however, who extensively described miliary sclerosis in 1907, and, after finding this neuropathology in 12 of 16 cases of senile dementia but not in any of 45 cases of progressive paralysis, 19 cases of functional psychosis nor 10 normal subjects, suggested that this neuropathology could be considered as a marker for senile dementia (46).

Meanwhile, in 1903, Bielschowsky improved upon the silver stain ("reazione nera") discovered by Golgi in 1873 (57), and made it possible for the first time to clearly visualize cellular components of neurons (5). While previously, using the carmine stain, it was only possible to make glial elements visible, Bielschowsky—using the silver stain—was able to identify threadlike structures within neurons, which he called neurofibrils (14). In 1907, using the Bielschowsky stain on the case that made him famous, Alois Alzheimer described a startling new pathology in the brain of a recently deceased woman who died a few years after developing a clinically unusual dementia at age 51. The novel neuropathological feature that Alzheimer observed consisted of tangles of fibrils within the cyptoplasm of neurons, which were stained in sharp definition by the silver impregnation. His description included the following excerpt:

> In sections prepared with the Bielschowsky silver method, remarkable changes in the neurofibrils appeared. In the interior of a cell that otherwise appeared normal, one or several fibrils stood out due to their extraordinary thickness and impregnability. At a later stage, many fibrils appeared, situated side by side and altered in the same way. Then they merged into dense bundles and gradually reached the surface of the cell. Finally, the nucleus and the cell disintegrated, and only a dense bundle of fibrils indicated the site where a ganglion cell had been.
>
> Since the fibrils could be stained with different dyes than normal, a chemical alteration of the fibrillar substance must have taken place. This then could be the reason why the fibrils survived the death of the cell . . . numerous ganglion cells, particularly in the upper cell layers, had disappeared entirely. . . . (13, p. 110) (For original German see (4)) (see Fig. 7).

In addition to the marked neurofibrillary tangles and accompanying neuronal degeneration, Alzheimer also noted the widespread presence of plaque pathology in the brain of this woman, similar to the pathology extensively described in senile dementia by Fischer (46) that same year: "Scattered through the entire cortex, especially in the upper layers, one found miliary foci that were caused by the deposition of a peculiar substance in the cerebral cortex . . ." (13, p. 110). (For original German see (46). For recent findings and discussion of this patient, see (53,56,91,107).)

The clinical and neuropathological presentation of this individual stood out quite distinctly from the vast number of previous cases examined by Alzheimer, as the dementias of his previous cases arose predominantly from neurosyphilis and vascular disease (brain ischemia). The young age of dementia onset, unusual clinical picture, and rapid course of disease progression, in addition to the unique neuropathological features and severity of the lesions (1 of 4 ganglion cells were found to contain tangles) did not permit this disease to be fitted to any of the known disease patterns of the time. Because this case did not fit the current nosological framework of mental disorders, and because he was well aware of the incompleteness of this framework, Alzheimer suggested that this case represented a previously undefined disease:

> we are apparently confronted with a distinctive disease process. An increasing number of unusual diseases have been discovered during the past few years. These observations show that we should not be satisfied to take a clinically unclear case and, by making great efforts, fit it into one of the known disease categories. Undoubtedly there are many more psychiatric diseases than are included in our textbooks. Often a subsequent histological examination would show the peculiarity of the case. Then gradually we would be able to separate individual diseases clinically from the large classes of diseases in our textbooks and define their clinical characteristics more precisely. (164, p. 110) (For original German see (4))

In the 5 years following Alzheimer's initial description, 11 similar cases of pre-senile dementia (i.e., onset before age 65) with accompanying neuropathological features of plaques and tangles were reported in the medical literature. It seemed that many other pathologists were willing to consider the condition described by Alzheimer to be, indeed, a unique disease entity, as suggested by Alzheimer, as several of these reports already referred to the condition as "Alzheimer's disease" (154). Official endorsement of this disease as a unique entity is most often attributed to Emil Kraepelin, however, the foremost psychiatrist in the world at the time (and today considered one of the founders of modern psychiatry), by his inclusion of "Alzheimer's disease" in the eighth edition of his *Textbook of Psychiatry*, published in 1910. Kraepe-

FIG. 7. Drawings by Gaetano Perusini, a student of Alzheimer, of neurons in various stages of neurofibrillar alteration (110), increasing in severity from left to right. The farthest right image shows a glia cell impinging on the neurofibrillar remains of a neuron.

lin's description of Alzheimer's Disease as a special subtype of senile dementia—presenile dementia—makes it clear, however, that Kraepelin himself was not entirely certain whether this was indeed a unique disease from aging and arteriosclerosis. In his textbook, he remarks that

> Alzheimer has described a unique group of cases with very severe cellular changes. . . . The post mortem findings, as given in Alzheimer's presentation, demonstrate to a certain extent the changes in the most severe forms of senile deterioration. . . . The clinical significance of this Alzheimer's Disease is still at the present time unclear. Although the anatomic findings would suggest the assumption that this is a matter of a particularly severe form of senile dementia, to some extent this is contradicted by the circumstance that the illness at times already begins at the end of the 40th year. In such cases one would at least have to assume a 'senium praecox' if it is not a matter, perhaps, of a unique disease process which is more or less independent of age. . . . Possibly connections exist with one or the other of the previously described pictures of presenile dementia. (135, p. 238) (For original German see (78))

The inclusion of Alzheimer's Disease in Kraepelin's textbook in 1910 seems rather premature in retrospect, as at the time Kraepelin probably only had five described cases upon which to form an opinion, and several authors have questioned Kraepelin's motives for doing so (5,7,154). It has even been suggested that the designation of the disease described by Alzheimer as "Alzheimer's disease" was largely due to competition between the neuropathological school located in Munich, with which Alzheimer and Kraepelin were affiliated, and the neuropathological school in Prague, with which Fischer and Pick were affiliated. As Amaducci (5) has pointed out, if presenile and senile dementia were to be considered one disease characterized by senile plaques and neurofibrillary tangles, there would be a rivalry for the appellation of the disease between Fischer, who extensively described plaques and associated neuronal alterations (see Fig. 8), and Alzheimer, who first described neurofibrillary tangles and also mentioned plaque pathology. It has thus been suspected by some that Kraepelin overlooked the uncertainty concerning the significance of tangles and downplayed the presence of plaque pathology in order to short-circuit the controversy at the advantage of his own school (5,7).

However, as remarked by Beach "it would be a disservice to Kraepelin to assume that he would have recognized Alzheimer's

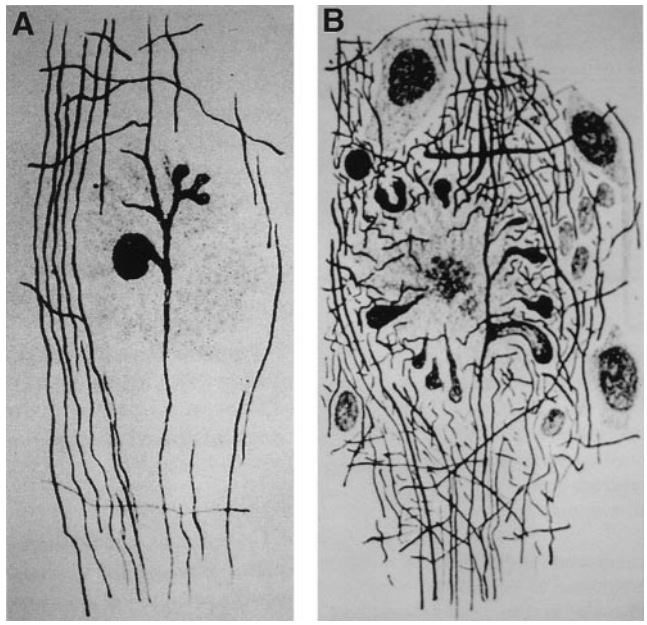


FIG. 8. Drawings by Oskar Fischer of the "proliferative changes in nerve fibers" induced by plaques (46). *A*) A neuronal process which passes over a plaque (seen in the background) has become dystrophic in the vicinity of the plaque. Fischer suggested there were stages in plaque progression: the smallest plaques were deduced to be the initial stage, and as the plaques enlarged, they were associated with greater numbers of abnormal fibers and sproutings. *B*) A plaque with a complexity of dystrophic neurites forming the characteristic "fibrillar network" of larger plaques.

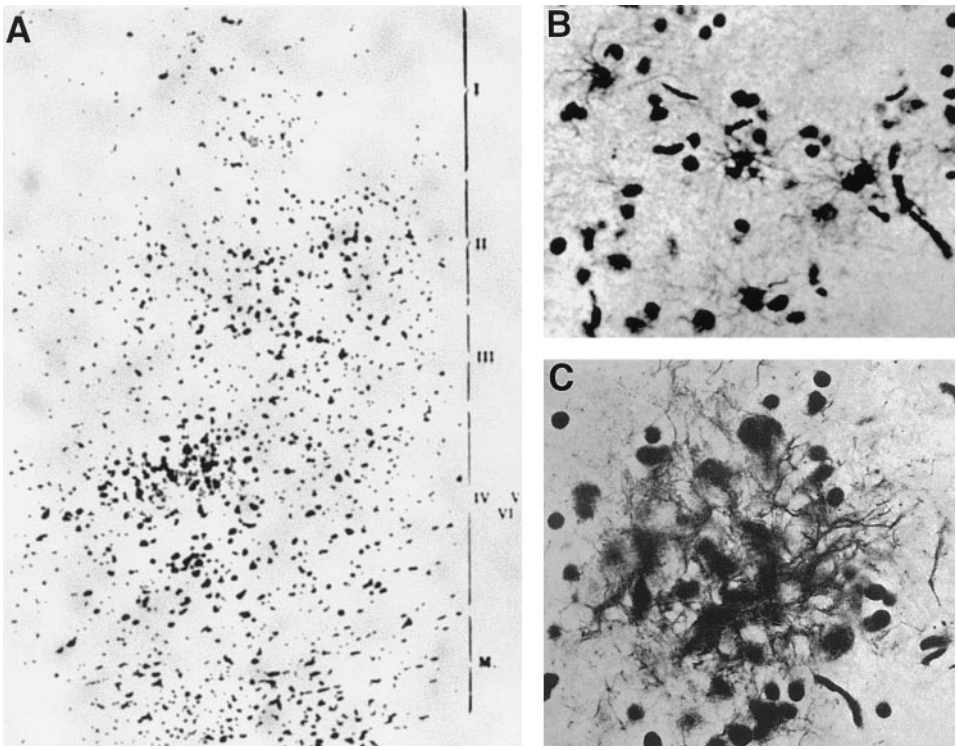


FIG. 9. Images prepared by Emil Kraepelin (78). The tendency to emphasize Kraepelin's involvement in the "politics of science" undermines his involvement as a basic scientist: *A*) Kraepelin observed that the significant loss of cortical cells in this "senile dementia" brain occurred without distortion of the cytoarchitecture. In areas of degenerated brain tissue, glial proliferation was often noted: in the frontal cortex shown in *B*), Kraepelin pointed out the presence of "a number of . . . glia nuclei, often disposed in little groups, next to which lie astrocytic forms with strikingly thin fibers, which are normally never seen here" (13, p. 71). Kraepelin indicated that *C* depicted glial fibers in a plaque; Fischer, however, considered this network to be composed of neuronal elements as opposed to glial elements.

disease solely as an act of academic favoritism" (7, p. 338). Indeed, Kraepelin himself extensively studied senile and pre-senile dementia cases at both the behavioral and histological level (78) (see Figs. 9 and 10); thus it is more likely that, in addition to holding Alzheimer's pathological assessments and opinions in very high regard (as Alzheimer had established himself as a preeminent neuropathologist over the previous 15 years), Kraepelin—like Alzheimer—was reluctant to consider that dementia at 50 was the same as dementia at 75. Whatever his motives and however equivocal his acceptance of Alzheimer's disease as a truly unique disease, Kraepelin's opinions were highly regarded, and were undoubtedly an important factor leading to the acceptance of the new disease.

In addition to analysis of pre-senile and senile dementia at the histological level, Kraepelin's behavioral observations (78) captured many of the abnormalities associated with senile dementia that today are recognized as basic features of the disease. In his 1910 textbook, Kraepelin summarized "the changes which the psychological personality undergoes in old age; the decrease in receptivity, decrease of mental resilience, restriction of sentimental relationships, slackening of energy, the development of obstinate unmanageability" (13, p. 49) (For original German see (78)). Kraepelin commented that

> In the most serious cases, the psychological alterations of old-age result in the disease pattern of dementia. The main feature of this disease consists of a gradually developing particular psychological weakness, in which perception and memory impairments appear as the most characteristic symptoms. The perception of external impressions becomes more error-prone and slowed . . . patient's perceptions seem to reach their full clarity only very gradually, and very often they fade away before reaching complete clarity. . . . (13, p. 50) (For original German see (78))

Kraepelin elaborated details of the types of memory impairments consistently encountered in senile dementia patients with great clarity, commenting that

> Routine memory impairments are considerable. Past events gradually vanish from their memory, although often events of their childhood are recalled in their mind with surprising vividness, then one memory follows another. Moreover, acquired abilities also gradually fail; the patient forgets foreign languages, cannot remember names or numbers, fails in mathematical problems. But in particular the memory of recent events starts to reveal numerous and incomprehensible gaps. . . . At the same time, the actual memories are undergoing arbitrary alterations; memory gaps are often filled up by inventions whose subjective origin is not clear even to the patient. . . . Often he mixes up various events separated in time and embellishes them with arbitrary invented additions. One can discover how, and with what inventiveness, the patient tries to hide his uncertainty about his real past. . . . One is conscious of a certain feeling of insecurity; while talking the patient corrects himself, will change his statements when other persons insist to the contrary, thinks he is mentally confused, totally mad. (13, pp. 50–51) (For original German see (78))

In addition to the memory deficits, Kraepelin described other areas where mental function is impaired. For example, he observed that

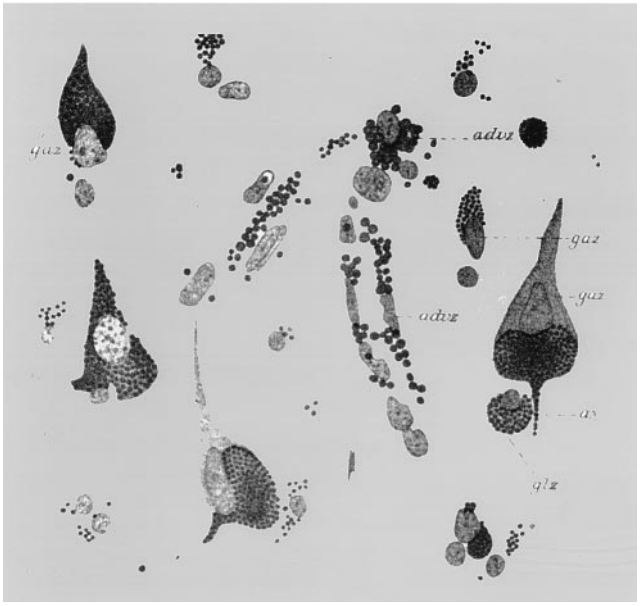


FIG. 10. Drawing by Emil Kraepelin of neuronal alterations observed in the cortex of an individual with a subtype of senile dementia, denoted "presbyophrenia" (78). The neuronal alteration depicted here was described as an extensive accumulation of "brownish-red stained fat granules which deposit and accumulate especially in the cytoplasm of the cells" (13, p. 68). Perusini also remarks on this "fatty degeneration" visible with hematoxylin-eosin staining. (Figure abbreviations from original text: glz, glial cells; gaz, ganglion cells; ax, axis cylinder; adv, adventitious cell.)

The processing of life experiences for the formation of independent opinions and conclusions, the critical evaluation of and attention to daily events, becomes gradually insufficient and insecure. In this way, in addition to a hopeless inability to learn, the patient develops a gullibility, which is the basis for the origin of delusion and fixed ideas. . . . The patients' emotional life is gradually devastated . . . their awareness either of suffering or of enjoying life decreases considerably. . . . In a series of cases the patients arrive at a very severe state of depression. . . . (13, pp. 51–53) (original German in (78))

To overview the progress made in a very short span of about 30 years, three distinct physiological abnormalities—a vascular dysfunction, a biochemical accumulation of a substance in the brain, and a neuronal change in brain cells—were discovered that seemed to be correlated with dementia phenomena in aged individuals. In addition, it seemed that new disease in the field of dementia had been discovered with the identification of Alzheimer's disease in individuals who developed "senile-type dementia" at a strikingly young age. The establishment of Alzheimer's disease as a disease distinct from senile dementia focused attention on the validity of this claim, and detailed observation at both the histological and behavioral levels of both diseases was undertaken, and would continue assiduously for several subsequent decades.

### 1910–1960s

Over the next several decades, attention was focused in particular on these newly highlighted pathological features—plaques and tangles—which had been identified in the brains of individuals with senile or presenile dementia. Specifically, researchers sought to understand the relevance of these features to Alzheimer's disease and senile dementia, as well as their pathological significance. Another central issue which remained an ever-present area of contention during this epoch concerned the validity of Alzheimer's disease as a separate disease category from senile dementia. In addition, the idea that that there may be a genetic component to Alzheimer's disease and senile dementia was discussed. (For a translated compilation of the seminal publications on Alzheimer's disease see reference (13). In addition, extensive reviews of the early theories have been written by Margolis (86) and McMenemey (97,99).)

#### *Diagnostic Value of the Pathological Features*

As the Bielschowsky stain and related stains came to be applied to investigate underlying pathologies of nearly all forms of mental illness, evidence rapidly accumulated that tangles were not specific to Alzheimer's disease. Tangles had already been identified in senile dementia before 1910; by 1957 they had been found in other dementia syndromes including Guam-Parkinsonism dementia complex and dementia pugilistica, as well as in diseases outside the realm of dementia, such as amyotrophic lateral sclerosis and post-encephalitic Parkinson's disease (97,99). The usefulness of plaques and tangles as diagnostic features in senile dementia and Alzheimer's disease became further questionable upon the identification of some cases of presenile and senile dementia that had no signs of either plaque or tangle pathology. Furthermore, the report by Gellerstedt in 1933 that over 80% of all non-demented individuals over age 65 had some senile plaques and tangles (50) added only further to the confusion. McMenemey placed the above findings in perspective, pointing out in 1940

That the pathological changes in this disease are not specific is generally agreed. . . . Nevertheless, the presence of *abundant* plaques and neurofibrillary alterations together with extensive atrophy of the neurones is found only in Alzheimer's disease and senile dementia. In the former, the changes are, in the main, both more severe and widespread. . . . In senile dementia on the other hand, plaques are usually less plentiful and neurofibrillary alterations are infrequent and may be absent. To this there are, of course, exceptions. . . . (98, p. 232)

On the other hand, other researchers in the field such as Critchley (33) and Jervis (66) came to the conclusion that plaque and tangle pathology was of minimal diagnostic value, and maintained that only clinical criteria formed a reliable basis for making a diagnosis of Alzheimer's disease or senile dementia. To make matters more complicated, however, the clinical diagnosis of Alzheimer's disease or senile dementia was also obscured at this time by the inability to resolve other disorders that presented similar clinical features to dementia, such as depression and paranoia—disorders which also commonly appear in late life (126).

#### *Significance of the Pathology: Source and Constitution*

While some researchers argued about the significance and specificity of tangles and plaques with respect to their usefulness as diagnostic features of Alzheimer's disease and senile dementia, others struggled to elucidate the significance of plaques and neurofibrillary tangles from a cellular point of view.

*Plaques.* The source and constitution of plaques was the subject of much controversy. The association of both neuronal and glial elements with plaques had been noted early on (see Fig. 11), and as a result, debate regarding the source of plaques centered around these two cell types. As reviewed by McMenemey (97), most of the earliest researchers including Blocq and Marinesco (20), Redlich (116), Alzheimer (4), Simchowicz (142), and Bielschowsky (15) believed that plaques had their origin in disintegrating glial reticulum. Others, however, such as Bonifiglio (22), Fischer (46), Perusini (110), and Fuller (49) opined that plaques arose from degenerating nerve fibers: damage to the nervous tissue was resulting in the deposition of some unknown pathological metabolic products. Later researchers including Lo-

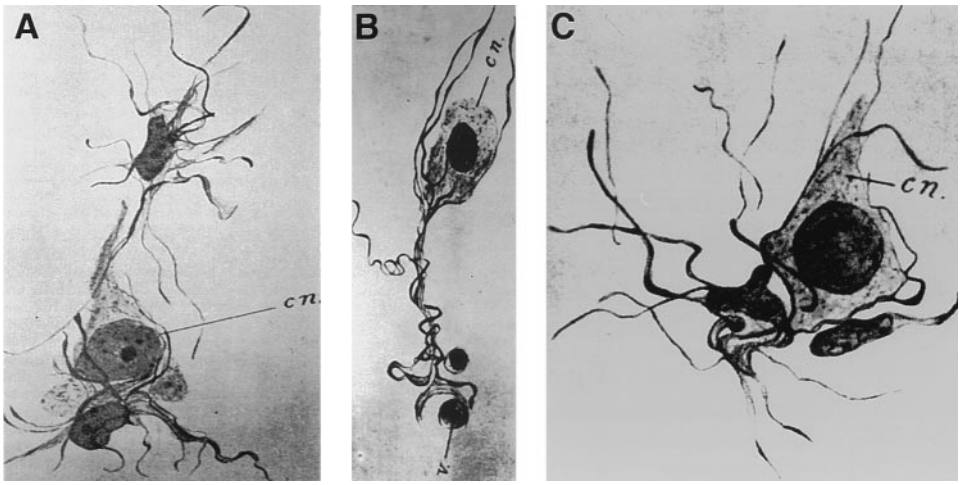


FIG. 11. Drawings by Gaetano Perusini (111). The extent to which glial elements were involved in the newly observed histopathologies was a highly contentious issue early on, and Perusini in particular was concerned by the inadequacy of available staining techniques for the definitive differentiation of glial elements from neuronal elements. *A, B* show clear cut cases of neurons (c.n.) "embraced by the elongations of surrounding astrocytes," by Weigert fixation and staining. In *C*, Perusini pointed out that Bielschowsky impregnation of glial fibrils which contact neurons (such as those in this image "embracing the base of the neuron on the right and left") may be "erroneously interpreted as altered neurofibrils, when their origin from a glial cell is not obvious" (13, p. 138).

wenberg (81) and Ferraro (44) were of less polarized opinions, and felt that in some circumstances plaques could originate from degenerating oligodendrocytes and microglia, while in other circumstances they might equally well arise from degenerating nerve cells or axons. Still others such as van Braunmühl (157) held that neither nerve nor glial cells had anything to do with the origin of plaques, but rather, that plaques were the result of condensing of the intracellular ground substance (97). In a 1940 overview of the literature, McMenemey diplomatically summed up the different views: "The origin of plaques has been variously accredited to disease of the nerve cells, axis cylinders, all types of glial cells and their processes, and even to the deposition of abnormal products of metabolism; perhaps there is something to be said for all of them." He later indicates, however, that "most authors . . . now believe that the role of the microglia and oligodendroglia is secondary. . ." (98, p. 226).

Just as the source of plaques was unclear, equally frustrating was the precise identification of its chemical make-up. Some headway was made in 1927 when Divry identified the substance in plaques as "amyloid" based on the property of green birefringence in polarized light following Congo red staining (38). The term "amyloid," however, was not very descriptive, as it was a general term devised in 1860 to describe "certain abnormal tissue aggregates that had staining properties similar to starch" (154, p. 77). Amyloid had been familiar to pathologists since the mid-19th century, who at that time had noted amyloid accumulation with age in certain peripheral organs, particularly the heart. Amyloidosis was most commonly known to accompany chronic infections such as tuberculosis, as well as chronic inflammation, such as in rheumatoid arthritis. No immediate link was made between Divry's 1927 observations on plaque content and the oft-observed association of amyloid with immune activation. Several decades later, however, when amyloid was confirmed to be the principal component of plaques, speculation arose that the deposition of amyloid in Alzheimer's disease might be attributable to a chronic infection, inflammatory disease, or auto-immune reaction (1,9,45, 72,162).

The development of the electron microscope, in conjunction with improved fixation, staining and embedding techniques in the 1950s, made possible the study of plaques at a new level of detail—the ultrastructural level. By the mid-1960s, ultrastructural studies confirmed that amyloid composed the central fibrillar core of plaques. In addition, the other main components of the plaques were now identified as being cellular perikarya, axons and dendrites filled with an excess of tangles, cell processes filled with dense bodies (later shown to be lysosomal in nature) as well as mitochondria in varying stages of alteration (77,79,150). While ultrastructural information provided more detailed knowledge of the plaques, it did not help to clarify either the source of the plaque material (though the finger was pointed at microglia), nor its significance.

*Neurofibrillary Tangles.* As for the issue of tangles, Alzheimer was of the opinion that these were the result of an alteration of the neurofibril. Neither Bielschowsky nor Divry were in agreement with Alzheimer, however. According to Bielschowsky (16), the position and convoluted shapes assumed by these tangles were too dissimilar to the appearance of normal neurofibrils, for these two to be related. Meanwhile Divry (39), with an eye for amyloid, was struck by the observation that the material forming these thick fibers had the staining and optical properties of amyloid. In his theory, amyloid material from the circulating fluids was being deposited on the surface of cells, forming fibrillar structures. Alzheimer's view was one of the most widely accepted ones, and several hypotheses arose to explain the neurofibrillary alteration. In the 1930s for example, studies by Alexander and Looney (3) suggested that these structures were "hypermineralized," while Bouman (23) proposed that the neurofibrillary alteration was an attempt at "hyperdifferentiation" (extensive sprouting), which was often seen in the early stages of regeneration of nerve fibers after injury. While these hypotheses did little to illuminate the cause of neurofibrillary tangle formation, the significance of tangles was clear: "It is impossible to believe that a nerve cell showing such a change in the structure of its neurofibrils, even making allowances for the fact that the change which we see is in autopsy or biopsy

material after fixation and impregnation, can be able to function in its usual way, and one presumes that such a cell is already effete" (99, p. 54).

Ultrastructural studies (i.e., electron microscopy) of Alzheimer biopsy specimens in the early 1960s made it clear that tangles were not composed of amyloid as believed by Divry. These studies further revealed that these presumed neurofilaments had the appearance of tubules, and that they had "periodicity," which suggested that these tubules were twisted into a helical structure (76,150,151). As a result of these ultrastructural studies, it was interpreted that "the neurofibrillary tangle in both disorders (senile dementia and Alzheimer's disease) is characterized by the twisted tubule that represents two neurofilaments joined together in a helical fashion with a periodicity of 800 Angstroms" (69, p. 217). These results were exciting, for they seemed to confirm what Alzheimer and others had long suspected, that these tangles were probably normal cytoskeletal elements that had developed an abnormal structure. This abnormal twisted structure, in turn, undoubtedly interfered with the neuron's proper functioning, and ultimately caused the neuron's death.

### *A Histopathology Characterized by Degenerative and Regenerative Aspects*

At both the naked-eye and microscope levels, one of the most striking features of the Alzheimer's-diseased and senile dementia brains was the degree of neuronal loss and resulting atrophy that had taken place (4,59,78). In light of this, it is not surprising that emphasis tended to be placed on the degenerative nature of the pathological processes taking place in these dementia brains. Some researchers, however, were struck by the degree to which neuronal processes often were intertwined with plaques and questioned whether regenerative or growth processes might also be occurring in this tissue. For example, Bouman remarked on this issue in 1934: "naturally the question arises whether all these formations [plaques, tangles]. . . are evidence of degeneration or regeneration, a question which Bielschowsky has discussed. He thinks it is impossible to regard them as degenerative processes" (23, p. 137). In addition, Cajal had proposed in 1928 that plaques were not merely sites of degeneration, but were also comprised of active neuronal involvement:

> It appears as if the sprouts had been attracted toward the region of the plaque under the influence of some special neurotropic substance. . . . They [sprouts] appear to have been preceded by the deposit of a certain stimulating substance which is expelled from the expansional protoplasm, and which is destroyed later . . . one may note that some of the new dendrites end in bulbs and tumefactions, which remind one of the buds of newly-formed axons. (27, p. 736) (see Fig. 12)

In addition, Cajal hypothesized on the causes of this neuronal sprouting, suggesting that "the regenerative act commences, and may even attain a certain strength, on condition that . . . toxins or special stimulative principles, as yet undetermined, invade the gray matter" (p. 736). While intriguing, little attention was paid to these astute observations at the time, as their significance was unclear and they seemed only to complicate the already complex picture of the pathogenesis of Alzheimer's disease/senile dementia. Interest in this area, however, was to resurge in the 1990s.

### *Alzheimer's Disease: Unique Disease from Senile Dementia?*

A recurrent issue which was fiercely debated for numerous decades was the question of whether Alzheimer's disease was really a unique disease entity from senile dementia. In his 1963 review on dementia, McMenemey (97) summarizes researchers' attempts to establish clinical and pathological criteria which would clearly delineate the two diseases. Clinically, for example, it was

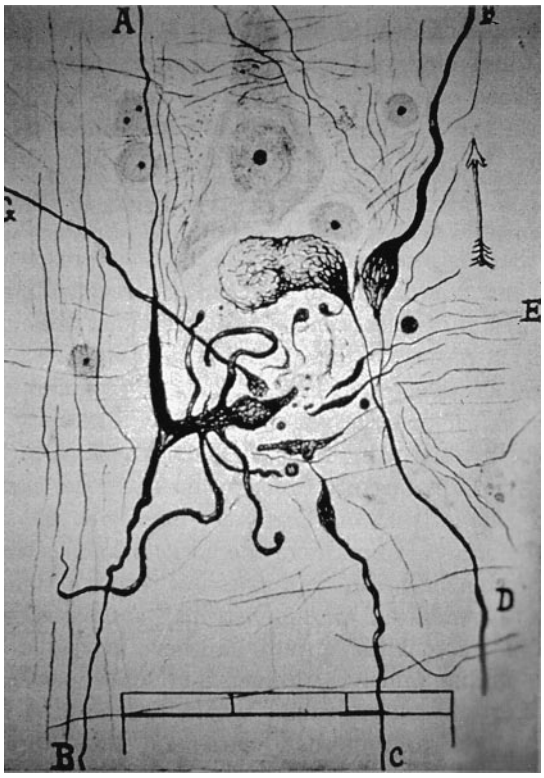


FIG. 12. Drawing by Simarro, a student of Cajal, of details of a plaque in Ramon y Cajal's book *Cajal's Degeneration and Regeneration of the Nervous System* (1). For Cajal, the neuronal changes induced by plaques were indicative of regenerative processes. "[A]. hypertrophied projection axon, next to the plaque, to which it sends a thick collateral ending in a bulb and numerous terminal branches; [D, G, F] fibers ending in buds of balls in the region of the plaque." Note the similarity to Fischer's rendition of plaques (Fig. 8); Fischer too observed the regenerative appearance of these neurons, however, he commented that "It would however be a little strange if we considered these formations simply as regeneration attempts, since these formations . . . appear uniquely in the brain, and are found . . . actually in masses in the senile atrophic brain" (13, p. 17). Figure printed from (27) by permission of Oxford University Press, Inc.

claimed that Alzheimer's disease was distinguished by "overactivity" (restlessness, wandering tendencies, irritability, and stereotyped movements). This distinction was clearly not supported: cases of "senile dementia" were noted to show motor unrest as well, and furthermore, Alzheimer's disease individuals were equally likely to be characterized by depression and apathy (42,58). Others held that focal symptoms of aphasia, agnosia, and apraxia were more common in Alzheimer's disease and could serve to differentiate between Alzheimer's disease and senile dementia (52,101); however, these symptoms were also noted in senile dementia cases. From the pathological perspective, those who favored the individuality of the two diseases maintained that the changes in Alzheimer's disease were more severe than those in senile dementia, and that the atrophy and neuron loss was greater (100,129). McMenemey has pointed out, however, that "these findings [more severe pathology in Alzheimer's disease] may be due to the fact that the presenile patient is better able to withstand the disease and to survive longer with it as compared with the senile patient" (97, p. 544). Many other criteria were proposed as distinguishing features of one or the other disease. However, as observations on more cases accumulated, none of these criteria

proved to be substantiated. Indeed, with time, the similarities in the clinical and pathological presentations of the majority of Alzheimer's disease and senile dementia cases only became more apparent. Clinically, both Alzheimer's disease and senile dementia showed a slowly progressive mental degeneration, characterized by failure of memory, disorientation, and confusion, which led eventually to profound dementia. Pathological examination revealed both to be characterized by general and widespread atrophy of the brain, with particularly severe atrophy of the frontal and occipital lobes, as well as of the hippocampus and fornix in the temporal lobe. Cortical layers 3 and 5 were noted to have the most severe cell loss as well as the greatest accumulation of pathology. In both diseases, plaques were always present, and were most profuse in the frontal and occipital lobes, the insula, and particularly the hippocampus. In general, neurofibrillary change was observed to run parallel with plaque formation in both Alzheimer's disease and senile dementia, affecting in particular the pyramidal cells of the frontal and temporal cortex, and quite severely Ammons horn of the hippocampus (97). Essentially the only tangible distinction between the two diseases which remained was that of age, and many researchers agreed that "if one accepts them [cases of senile dementia], in spite of their late age of onset, as instances of Alzheimer's disease, then few cases remain to be labeled senile dementia" (97, p. 543). While it was generally accepted by the 1960s that there was essentially no evidence upon which to base a distinction between the two disease categories, the two were to remain discrete for nearly two additional decades, at which time they were finally united, under the name of Senile Dementia of the Alzheimer's type (SDAT) (69,70).

### *Genetic Component*

By the 1930s, many investigators were beginning to question whether there was a hereditary component to Alzheimer's disease and senile dementia. In the short period from 1929–1932, three investigators identified what appeared to be familial patterns of inheritance in two generations: Flügel (47) identified three cases of possible Alzheimer's disease/senile dementia; Schottky (136) identified two cases; and Lowenberg (82) identified five cases, where in each family, one case was autopsy-confirmed to be Alzheimer's disease or senile dementia. In the subsequent decades, numerous other reports of a familial incidence accumulated (43). Confirmation of a genetic component to Alzheimer's disease and senile dementia only became possible many decades later however, when more in-depth genetic analysis techniques became available.

Clearly, these first 60 years of research on Alzheimer's disease were a time of intense debate and disagreement concerning nearly all issues pertaining to this disease. A more orderly picture and more significant correlation of pathology to the clinical diagnosis began to emerge after 1960, as a result of the efforts of Roth, Blessed, and Tomlinson, who introduced the application of stricter criteria in clinical diagnosis, as well as quantitative methods in the study of the postmortem brain (124–128). These steps were fundamental, for they emphasized the fact that similar mental changes could be caused by a variety of underlying etiologies. As a result, sharper boundaries were defined between different subtypes of senile dementia, which would allow a clearer definition and conceptualization of Alzheimer's disease to emerge. In addition, these advances allowed the confusing issue concerning the presence of pathology in non-demented individuals to be resolved; examination of the quantity and distribution throughout the brain of plaques and tangles, in both demented and nondemented individuals, revealed a correlation between the degree of pathology and the degree of dementia (127,128). Thus by the end of the 1960s, a basic conceptualization of the defining features of Alzheimer's disease had been established, and the foundations for future directions of research had been laid.

## 1970S–PRESENT

The last 25 years have marked a new era in progress in the field of Alzheimer's disease. As a result of a massively expanded research effort beginning in the early 1980s, this disease has been scrutinized from innumerable angles, exponentially augmenting both our understanding of this disease as well as our appreciation of its complexity. Biochemical, molecular, genetic, and epidemiological approaches, among others, have expanded knowledge of the neurochemical, neuropathological, and genetic aspects of Alzheimer's disease (for reviews, see (8,24,25,30,36,37,41,63,68,71,75,95,106,108,119,120,137,138,147,151,154,155,166,167,169)). In turn, the elucidation of numerous fundamental characteristics of this disease has enabled hypotheses about the disease mechanisms to be formulated and tested, and applied to the development of therapeutic agents. While still in their infancy currently in the 1990s, these approaches are proving successful, as today, therapeutic agents for the treatment of symptoms are available, preventative measures to delay the disease onset are being elucidated, several risk factors for Alzheimer's disease have been identified, and improved diagnostic strategies are emerging. For example, the identification of an extensive disruption of cholinergic input to the forebrain has led to the development and FDA approval of two anti-cholinesterase drugs which improve cognition and function in many Alzheimer's patients, Tacrine and Aricept (21,32,149). In addition, secondary disease mechanisms including inflammatory mechanisms (25,28,41,61,68,83,94,106,108,109,120,141), oxidative damage (8,51,90,95,143,148), and inappropriate apoptosis (30,31,51,80,104) have recently been identified as factors contributing to the pathogenesis of Alzheimer's disease. The identification of these secondary disease mechanisms has led to the development of preventative measures to delay the disease onset, including non-steroidal anti-inflammatory drugs (25,118,119), and anti-oxidants such as selegeline and vitamin E (87,132). The recognition that Alzheimer's disease afflicts a greater proportion of women than men (which had been commented upon as early as the 1940s (103)), and the recognition that nearly all of these women are post-menopausal, has led to the identification of estrogen treatment as an effective strategy delaying the disease onset in women (17,40,60,73,93,114). Finally, improved diagnosis of Alzheimer's disease has been achieved by supplementing traditionally derived psychometric information with genetic information, such as ApoE genotyping (29,92,113,122,123,133), as well as with information about brain anatomy and functioning derived from the application of imaging techniques, such as MRI, SPECT, and PET (2,19,26,35,67,74,89,102,105,130,131,145–147,160,161,163,169). While the exact pathogenesis and effective treatment of Alzheimer's disease still remains elusive at this time, there has been a tremendous amount of progress in the last 25 years in identifying possible underlying pathogenic mechanisms involved in this disease, as well as in the development of potential therapeutic agents tackling the disease progression. With a renewed historical perspective on dementia spanning centuries, and in light of the remarkably rapid pace of recent discoveries, future progress is likely to continue at an accelerated pace, bringing with it increased understanding of the mechanisms of this disease as well as potentially effective treatment options.

## SUMMARY

Although senile dementia has been a recognized condition of aged individuals since at least the time of Pythagoras in the 7th

century B.C., because it was dismissed as an inevitable feature of aging, it remained largely an uninvestigated disorder until the 19th century. Most references to mental deterioration in old age which predate the 19th century referred to a larger group of dementia conditions than what is included in today's narrower definition. It was only with Pinel and Esquirol's introduction of a scientific approach to clinical observation and the systematized classification of mental disorders in the mid-19th century that senile dementia began to be differentiated from other dementias, and was established as its own defined class of mental disorder. It was probably about this time that the realization that senile dementia was not inevitable and that it was an abnormal form of aging began to emerge.

The first etiological basis for senile dementia was discovered at the end of the 19th century, with the observation of numerous stroke foci in the brain characterized by areas of focal cell death. Advances in microscopy and the invention of new histochemical stains at the turn of 20th century revealed a brain pathology consisting of the accumulation of a biochemical substance into widespread plaques, abnormal cytoskeletal changes within neurons, glial cell activation and proliferation, and neuronal death accompanying both plaques and tangles. The discovery by Alzheimer of neurofibrillary tangles in a middle-aged woman who presented a rapid course of dementia led several influential individuals, such as Kraepelin and Alzheimer, to believe that a new disease had been discovered. The rate of progress in understanding the causes of dementia idled for about four decades after the establishment of Alzheimer's disease as a presenile dementia distinct from senile dementia, due to confusion regarding the significance of the different pathologies, the validity of a distinction between Alzheimer's disease and senile dementia, and the differentiation of normal aging from the disease process of senile dementia. These issues were resolved by 1) establishing that there were varied pathological features all contributing to dementia and that they constituted different subtypes of dementia, 2) recognizing that Alzheimer's disease and senile dementia were essentially the same disease with different ages of onset, and 3) correlating the extent of pathology throughout the brain, with the degree of dementia exhibited by the individual.

The careful and astute observations of the early researchers from the first half of the 20th century set the foundation for future progress in understanding Alzheimer's disease. These individuals identified with remarkable accuracy the basic characteristics of this disease as well as discussed issues in the pathology which are still not resolved today. While Alzheimer's disease was recognized as a troublesome disorder already in the early 1900s, today it has become a major medical problem nearing catastrophic levels; increased longevity has led to a steadily increasing population of individuals over age 65, and thus there are ever greater numbers of individuals at risk for, and afflicted with, this disease. Alzheimer's disease is today recognized as the fourth or fifth leading cause of death in the U.S., and is among the most intensely researched areas of science. The money and research which have been invested in understanding this disorder in just the last 20 years has already rewarded us with the first steps toward effective treatment and prevention, and the future holds promise for even more remarkable progress.

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## REFERENCES

1. Amyloidosis of Alzheimer's disease: A clue to ageing? Lancet 2:598–9; 1970.
2. Albert, M. S. Cognitive and neurobiologic markers of early Alzheimer disease. Proc. Natl. Acad. Sci. USA 93:13547–51; 1996.
3. Alexander, L.; Looney, J. M. Physicochemical properties of brain, especially in senile dementia and cerebral edema. Arch. Neurol. Psychiat. 40:877–902; 1938.
4. Alzheimer, A. Uber eine eigenartige Erkrankung der Hirnrinde. Allg. Z. Psychiat. Psych.-Gericht. Med. 64:146–148; 1907.
5. Amaducci, L. A.; Rocca, W. A.; Schoenberg, B. S. Origin of the distinction between Alzheimer's disease and senile dementia: How history can clarify nosology. Neurology 36:1497–1499; 1986.
6. Barrough, P. The methode of phisicke (1583). In: Hunter, R.; Macalpine, I., eds. Three Hundred Years of Psychiatry (1535–1860): A history presented in selected English texts. Hartsdale, New York: Carlisle Publishing; 1982:24–28.
7. Beach, T. G. The history of Alzheimer's disease: 3 debates. J. Hist. Med. Allied Sci. 42:327–349; 1987.
8. Beal, M. F. Mitochondria, free radicals, and neurodegeneration. Curr. Opin. Neurobiol. 6:661–6; 1996.
9. Behan, P. O.; Feldman, R. G. Serum proteins, amyloid and Alzheimer's disease. J. Am. Geriatr. Soc. 18:792–7; 1970.
10. Bernal, J. D. The Emergence of Science. Cambridge: M.I.T. Press; 1965.
11. Berrios, G. E. Dementia during the seventeenth and eighteenth centuries: A conceptual history. Psychol. Med. 17:829–837; 1987.
12. Berrios, G. E. Dementia: Historical overview. In: Burns, A.; Levy, R., eds. Dementia. London: Chapman and Hall; 1994:5–19.
13. Bick, K.; Amaducci, L.; Pepeu, G. The Early Story of Alzheimer's Disease. Translation of the historical papers. Padova, Italy: Liviana Press; 1987.
14. Bielschowsky, M. Die Ziele bei Impregnation der Neurofibrillen. Neurol. Centralbl. 22:997–1006; 1903.
15. Bielschowsky, M. Zur Kenntnis der Alzheimerschen Krankheit (präsenilen Demenz mit Herdsymptomen). J. Psychol. Neurol. Lpz. 18:273–292; 1911.
16. Bielschowsky, M. Histopathology of nerve cells. In: Penfield, W., eds. Penfield's Cytology and Cellular Pathology of the Nervous System. New York: Hafner Publishing Co.; 1932:147–188.
17. Birge, S. J. The role of estrogen in the treatment of Alzheimer's disease. Neurology S36–41; 1997.
18. Black, J. E.; Isaacs, K. R.; Greenough, W. T. Usual vs. successful aging: Some notes on experiential factors [comment]. Neurobiol. Aging 12:325–8; discussion 352–5; 1991.
19. Blesa, R.; Mohr, E.; Miletich, R. S.; Hildebrand, K.; Sampson, M.; Chase, T. N. Cerebral metabolic changes in Alzheimer's disease: Neurobehavioral patterns. Dementia 7:239–45; 1996.
20. Blocq, P.; Marinesco, G. Sur les lésions et la pathogénie de l'épilepsie dite essentielle. Semaine Médical 12:445–6; 1892.
21. Boller, F.; Forette, F. Alzheimer's disease and THA: A review of the cholinergic theory and of preliminary results. Biomed. Pharmacother. 43:487–91; 1989.
22. Bonifiglio, F. Di speciali reperti in un caso di probabile sifilide cerebrale. Rivista Sperim. Freniatria 34:196–206; 1908.
23. Bouman, L. Senile plaques. Brain 57:128–142; 1934.
24. Braak, H.; Braak, E. Staging of Alzheimer's disease-related neurofibrillary changes. Neurobiol. Aging 16:271–8; discussion 278–84; 1995.
25. Breitner, J. C. Inflammatory processes and antiinflammatory drugs in Alzheimer's disease: A current appraisal. Neurobiol. Aging 17:789–94; 1996.
26. Brooks, D. J. Functional imaging techniques in the diagnosis of

non-Alzheimer dementias. J. Neural. Transm. Suppl. 47:155–67; 1996.
27. Cajal, R. y.; Cajal's Degeneration & Regeneration of the Nervous System. New York: Oxford University Press, Inc.; 1928.
28. Chen, S.; Frederickson, R. C.; Brunden, K. R. Neuroglial-mediated immunoinflammatory responses in Alzheimer's disease: Complement activation and therapeutic approaches. Neurobiol. Aging 17: 781–7; 1996.
29. Corder, E. H.; Saunders, A. M.; Strittmatter, W. J.; Schmechel, D. E.; Gaskell, P. C.; Small, G. W.; Roses, A. D.; Haines, J. L.; Pericak, V. M. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families [see comments]. Science 261:921–3; 1993.
30. Cotman, C. W.; Anderson, A. J. A potential role for apoptosis in neurodegeneration and Alzheimer's disease. Mol. Neurobiol. 10:19–45; 1995.
31. Cotman, C. W.; Su, J. H. Mechanisms of neuronal death in Alzheimer's disease. Brain Pathol. 6:493–506; 1996.
32. Crismon, M. L. Tacrine: First drug approved for Alzheimer's disease. Ann. Pharmacother. 28:744–51; 1994.
33. Critchley, M. The neurology of old age, part III. Lancet 1:1331–1337; 1931.
34. Cullen, W. First lines in the practice of physic (1784). In: Hunter, R.; Macalpine, I., eds. Three Hundred Years of Psychiatry (1535–1860): A history presented in selected English texts. Hartsdale, NY: Carlisle Publishing; 1982:473–479.
35. Cummings, J. L. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. Neurology S10–6; 1997.
36. Davies, P. Strategies for the development of therapeutics for Alzheimer's disease. Neurobiol. Aging 15:S53–4; 1994.
37. Dickson, D. W. The pathogenesis of senile plaques. J. Neuropathol. Exp. Neurol. 56:321–39; 1997.
38. Divry, P. Etude histochimique des plaques séniles. J. Belge. Neurol. 27:643–657; 1927.
39. Divry, P. De la nature de l'alteration fibrillaire d'Alzheimer. J. Belge. Neurol. Psychiat. 34:197–201; 1934.
40. Doraiswamy, P. M.; Bieber, F.; Kaiser, L.; Krishnan, K. R.; Reuning, S. J.; Gulanski, B. The Alzheimer's Disease Assessment Scale: Patterns and predictors of baseline cognitive performance in multicenter Alzheimer's disease trials. Neurology 48:1511–7; 1997.
41. Eikelenboom, P.; Veerhuis, R. The role of complement and activated microglia in the pathogenesis of Alzheimer's disease. Neurobiol. Aging 17:673–80; 1996.
42. English, W. H. Alzheimer's disease. Psychiat. Quart. 16:91–106; 1942.
43. Feldman, R. G.; Chandler, A. C.; Levy, L. L.; Glaser, G. H. Familial Alzheimer's disease. Neurology 13:811–824; 1963.
44. Ferraro, A. The origin and formation of senile plaques. Arch. Neurol. Psychiatr. 25:1042–1062; 1931.
45. Field, E. J. Amyloidosis, Alzheimer's disease, and ageing. Lancet 2:780–1; 1970.
46. Fischer, O. Miliare Nekrosen mit drusigen Wucherungen der Neurofibrillen, eine regelmässige Veränderung der Hirnrinde bei seniler Demenz. Mschr. Psychiat. Neurol. 22:361–372; 1907.
47. Flügel, F. E. Zur Diagnostik der Alzheimerschen Krankheit. Z. ges. Neurol. Psychiat. 120:783–787; 1929.
48. Forstl, H.; Howard, R. Recent studies on dementia senilis and brain disorders caused by atheromatous vascular disease: by A. Alzheimer, 1898. Alz. Dis. Assoc. Dis. 5:257–64; 1991.
49. Fuller, S. C. A study of the miliary plaques in brains of the aged. Am. J. Insan. 68:147–217; 1911.
50. Gellerstedt, N. Zur Kenntnis der Hirnveränderungen bei der normalen Altersinvolution. Uppsala. Lak. Foren. Forrh. 38:193–408; 1933.
51. Gorman, A. M.; McGowan, A.; O'Neill, C.; Cotter, T. Oxidative stress and apoptosis in neurodegeneration. J. Neurol. Sci. 45–52; 1996.
52. Grünthal, E. In: Bumke, O., ed. Handbuch der Geistenkrankheiten. Berlin: 1930:638.
53. Gurwitz, D. Auguste D and Alzheimer's disease [letter]. Lancet 350:298; 1997.
54. Hachinski, V. Binswanger's disease: Neither Binswanger's nor a disease [editorial]. J. Neurol. Sci. 103:1; 1991.
55. Halpert, B. P. Development of the term "senility" as a medical diagnosis. Minn. Med. 66:421–4; 1983.
56. Hamann, C. Auguste D and Alzheimer's disease [letter]. Lancet 350:297–8; 1997.
57. Haymaker, W.; Schiller, F.; The Founders of Neurology. Springfield, Illinois: Charles C. Thomas; 1970.
58. Hemphill, R. E.; Stengel, E. Alzheimer's disease with predominating crossed cerebro-cerebellar hemiatrophy. J. Neurol. Psychiat. 4:97–106; 1941.
59. Henderson, D. K.; Maclachlan, S. H. Alzheimer's disease. J. Ment. Sci. 76:646–661; 1930.
60. Henderson, V. W. The epidemiology of estrogen replacement therapy and Alzheimer's disease. Neurology S27–35; 1997.
61. Hull, M.; Fiebich, B. L.; Lieb, K.; Strauss, S.; Berger, S. S.; Volk, B.; Bauer, J. Interleukin-6 (IL-6)-associated inflammatory processes in Alzheimer's disease: New therapeutic options. Neurobiol. Aging 17:795–800; 1996.
62. Hunter, R.; Macalpine, I.. Three Hundred Years of Psychiatry (1535–1860): A history presented in selected English texts. Hartsdale, New York: Carlisle Publishing; 1982.
63. Hyman, B. T. Alzheimer's disease or Alzheimer's diseases? Clues from molecular epidemiology [editorial]. Ann. Neurol. 40:135–6; 1996.
64. Inouye, S. K.; Albert, M. S.; Mohs, R.; Sun, K.; Berkman, L. F. Cognitive performance in a high-functioning community-dwelling elderly population. J. Gerontol. 48:M146–51; 1993.
65. Jameson, T. Essays on the Changes of the Human Body and its Different Ages. London: J. G. Bernard; 1811.
66. Jervis, G. A.; Soltz, S. E. Alzheimer's disease—the so-called juvenile type. Am. J. Psychiatry 93:39–56; 1936.
67. Jonkman, E. J. The role of the electroencephalogram in the diagnosis of dementia of the Alzheimer type: An attempt at technology assessment. Neurophysiol. Clin. 27:211–9; 1997.
68. Kalaria, R. N.; Harshbarger, K. M.; Cohen, D. L.; Premkumar, D. R. Molecular aspects of inflammatory and immune responses in Alzheimer's disease. Neurobiol. Aging 17:687–93; 1996.
69. Katzman, R. Editorial: The prevalence and malignancy of Alzheimer disease. A major killer. Arch. Neurol. 33:217–8; 1976.
70. Katzman, R. Senile dementia of the Alzheimer type—defining a disease. In: Maddox, G. L.; Auld, E., eds. Proceedings of seminars 1976–1980. Durham, N.C.: Duke University council on Aging; 1981:19–40.
71. Katzman, R.; Galasko, D.; Saitoh, T.; Thal, L. J.; Hansen, L. Genetic evidence that the Lewy body variant is indeed a phenotypic variant of Alzheimer's disease. Brain Cogn. 28:259–65; 1995.
72. Katzman, R.; Suzuki, K. A search for a chemical correlate of amyloid in senile plaques of Alzheimer's disease. Trans. Am. Neurol. Assoc. 89:17–20; 1964.
73. Kawas, C.; Resnick, S.; Morrison, A.; Brookmeyer, R.; Corrada, M.; Zonderman, A.; Bacal, C.; Lingle, D. D.; Metter, E. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: The Baltimore Longitudinal Study of Aging. Neurology 48:1517–21; 1997.
74. Kesslak, J. P.; Nalcioglu, O.; Cotman, C. W. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease [see comments]. Neurology 41:51–4; 1991.
75. Khachaturian, Z. S. Calcium hypothesis of Alzheimer's disease and brain aging. Ann. N. Y. Acad. Sci. 747:1–11; 1994.
76. Kidd, M. Paired helical filaments in electron microscopy of Alzheimer's disease. Nature 197:192–3; 1963.
77. Kidd, M. Alzheimer's disease—an electron microscopy of Alzheimer's disease. Brain 87:307–320; 1964.
78. Kraepelin, E. Das senile und präsenile Irresein. eds. Psychiatrie: Ein Lehrbuch für Studierende und Arzte. Leipzig: Johann Ambrosius Barth; 1910:533–632.
79. Krigman, M. R. Alzheimer's presenile dementia. Lab. Invest. 14: 381–396; 1965.
80. Kusiak, J. W.; Izzo, J. A.; Zhao, B. Neurodegeneration in Alzheimer disease. Is apoptosis involved? Mol. Chem. Neuropathol. 28:153–62; 1996.

81. Lowenberg, K. Die Histopathologie und Histogenese der Plaques Seniles. Z. ges. Neurol. Psychiat. 98:549; 1925.
82. Lowenberg, K.; Waggoner, R. W. Familial organic psychosis (Alzheimer's type). Arch. Neurol. Psychiat. 31:737–754; 1934.
83. Ma, J.; Brewer, H. J.; Potter, H. Alzheimer A beta neurotoxicity: Promotion by antichymotrypsin, ApoE4; inhibition by A β-related peptides. Neurobiol. Aging 17:773–80; 1996.
84. Magner, L. N.; A History of Medicine. New York, New York: Marcel Dekker, Inc; 1992.
85. Mahendra, B.; Dementia, a Survey of the Syndrome of Dementia. Lancaster, England: MTP Press Limited; 1987.
86. Margolis, G. Senile cerebral disease. A critical survey of traditional concepts based upon observations with newer techniques. Lab. Invest. 8:335–370; 1959.
87. Marx, J. Searching for drugs that combat Alzheimer's [news]. Science 273:50–3; 1996.
88. Mast, H.; Tatemichi, T. K.; Mohr, J. P. Chronic brain ischemia: The contributions of Otto Binswanger and Alois Alzheimer to the mechanisms of vascular dementia. J. Neurol. Sci. 132:4–10; 1995.
89. Masterman, D. L.; Mendez, M. F.; Fairbanks, L. A.; Cummings, J. L. Sensitivity, specificity, and positive predictive value of technetium 99-HMPAO SPECT in discriminating Alzheimer's disease from other dementias. J. Geriatr. Psychiatry Neurol. 10:15–21; 1997.
90. Mattson, M. P. Degenerative and protective signaling mechanisms in the neurofibrillary pathology of AD. Neurobiol. Aging 16:447–57; discussion 458–63; 1995.
91. Maurer, K.; Volk, S.; Gerbaldo, H. Auguste D and Alzheimer's disease. Lancet 349:1546–9; 1997.
92. Mayeux, R.; Ottman, R.; Maestre, G.; Ngai, C.; Tang, M. X.; Ginsberg, H.; Chun, M.; Tycko, B.; Shelanski, M. Synergistic effects of traumatic head injury and apolipoprotein-ϵ 4 in patients with Alzheimer's disease [see comments]. Neurology 555–7; 1995.
93. McBee, W. L.; Dailey, M. E.; Dugan, E.; Shumaker, S. A. Hormone replacement therapy and other potential treatments for dementias. Endocrinol. Metab. Clin. North Am. 26:329–45; 1997.
94. McGeer, P. L.; McGeer, E. G. The inflammatory response system of brain: Implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res. Brain Res. Rev. 21:195–218; 1995.
95. McGeer, P. L.; McGeer, E. G. Anti-inflammatory drugs in the fight against Alzheimer's disease. Ann. N. Y. Acad. Sci. 777:213–20; 1996.
96. McGrew, R. E. Encyclopedia of Medical History. USA: Roderick E. McGrew; 1985.
97. McMenemey, W. The dementias and progressive diseases of the basal ganglia. In: Greenfield, J.; Blackwood, W.; Mcmenemey, W.; et al., eds. Greenfield's Neuropathology. London: Arnold; 1963:520–546.
98. McMenemey, W. H. Alzheimer's disease. J. Neurol. Psych. 3:211–240; 1940.
99. McMenemey, W. H. Dementia in Middle Age: A critical review. J. Neurol. Psych. 4:48–79; 1941.
100. Mutrux, S. Contribution a l'étude des corrélations anatomo-cliniques dans les démences dégénératives et les démences artérioscléreuses. Mschr. Psychiat. Neurol. 125:19–38; 1953.
101. Mutrux, S. Contribution à l'étude histologique differentiale de la démence sénile et de la maladie d'Alzheimer. Mschr. Psychiat. Neurol. 136:157–194; 1958.
102. Newberg, A. B.; Alavi, A. The study of neurological disorders using positron emission tomography and single photon emission computed tomography. J. Neurol. Sci. 135:91–108; 1996.
103. Newton, R. D. The identity of Alzheimer's disease and senile dementia and their relationship to senility. Alzheimer's Disease and Senile Dementia 225–248; 1947.
104. Nishimoto, I.; Okamoto, T.; Giambarella, U.; Iwatsubo, T. Apoptosis in neurodegenerative diseases. Adv. Pharmacol. 41:337–68; 1997.
105. Nordberg, A. Application of PET in dementia disorders. Acta Neurol. Scand. Suppl. 168:71–6; 1996.
106. O'Banion, M. K.; Finch, C. E. Inflammatory mechanisms and anti-inflammatory therapy in Alzheimer's disease [editorial]. Neurobiol. Aging 17:669–71; 1996.
107. O'Brien, C. Auguste D and Alzheimer's disease [news]. Science 273:28; 1996.
108. Pasinetti, G. M. Inflammatory mechanisms in neurodegeneration and Alzheimer's disease: The role of the complement system. Neurobiol. Aging 17:707–16; 1996.
109. Pereira, H. A.; Kumar, P.; Grammas, P. Expression of CAP37, a novel inflammatory mediator, in Alzheimer's disease. Neurobiol. Aging 17:753–9; 1996.
110. Perusini, G. Uber klinisch und histologisch eigenartige psychische Erkrankungen des späteren Lebensalters. Histologische und histopathologische Arbeiten 3:297–351; 1910.
111. Perusini, G. Sul valore nosografico di alcuni reperti istopatologici caratteristici per la senilitá. Rivista italiana di Neuropathologia, Psichiatria ed Elettroterapia 4:193–213; 1911.
112. Pinel, P. A treatise on insanity. In: Hunter, R.; Macalpine, I., eds. Three Hundred Years of Psychiatry (1535–1860). Hartsdale, NY: Carlisle Publishing, Inc.; 1806:602–610.
113. Post, S. G.; Whitehouse, P. J.; Binstock, R. H.; Bird, T. D.; Eckert, S. K.; Farrer, L. A.; Fleck, L. M.; Gaines, A. D.; Juengst, E. T.; Karlinsky, H.; Miles, S.; Murray, T. H.; Quaid, K. A.; Relkin, N. R.; Roses, A. D.; St George-Hyslop, P.; Sachs, G. A.; Steinbock, B.; Truschke, E. F.; Zinn, A. B. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. JAMA 227: 832–6; 1997.
114. Rankin, L. Alzheimer's disease: New horizons in diagnosis and treatment. Iowa Med. 87:199–201; 1997.
115. Rath, G. Neural pathology: A pathogenic concept of the 18th and 19th centuries. Bull. Hist. Med. 33:526–541; 1959.
116. Redlich, E. Ueber miliare Sklerose der Hirnrinde bei seniler Atrophie. J. Psychiat. Neurol. 17:208–216; 1898.
117. Rhodes, P. An Outline History of Medicine. Cambridge, England: University Press; 1985.
118. Rich, J. B.; Rasmusson, D. X.; Folstein, M. F.; Carson, K. A.; Kawas, C.; Brandt, J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease [see comments]. Neurology 45:51–5; 1995.
119. Rogers, J.; Kirby, L. C.; Hempelman, S. R.; Berry, D. L.; McGeer, P. L.; Kaszniak, A. W.; Zalinski, J.; Cofield, M.; Mansukhani, L.; Willson, P.; et al. Clinical trial of indomethacin in Alzheimer's disease. Neurology 43:1609–11; 1993.
120. Rogers, J.; Webster, S.; Lue, L. F.; Brachova, L.; Civin, W. H.; Emmerling, M.; Shivers, B.; Walker, D.; McGeer, P. Inflammation and Alzheimer's disease pathogenesis. Neurobiol. Aging 17:681–6; 1996.
121. Roses, A. D. Apolipoprotein E affects the rate of Alzheimer disease expression: β-amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease [see comments]. J. Neuropathol. Exp. Neurol. 53:429–37; 1994.
122. Roses, A. D. Apolipoprotein E genotyping in the differential diagnosis, not prediction, of Alzheimer's disease [see comments]. Ann. Neurol. 38:6–14; 1995.
123. Roses, A. D.; Saunders, A. M. APOE is a major susceptibility gene for Alzheimer's disease. Curr. Opin. Biotechnol. 5:663–7; 1994.
124. Roth, M. The natural history of mental disorder in old age. J. Ment. Sci. 101:281–301; 1955.
125. Roth, M. The association of clinical and neurological findings and its bearing on the classification and aetiology of Alzheimer's disease. Brit. Med. Bull. 42:42–50; 1986.
126. Roth, M.; Morrissey, J. D. Problems in the diagnosis and classification of mental disease in old age with a study of case material. J. Ment. Sci. 99:439–448; 1952.
127. Roth, M.; Tomlinson, B. E.; Blessed, G. Correlation between scores for dementia and counts of 'senile plaques' in cerebral gray matter of elderly subjects. Nature 209:109–10; 1966.
128. Roth, M.; Tomlinson, B. E.; Blessed, G. The relationship between quantitative measures of dementia and of degenerative changes in the cerebral gray matter of elderly subjects. Proc. R. Soc. Med. 60:254–60; 1967.
129. Rothschild, D.; Kasanin, J. Clinicopathologic study of Alzheimer's disease: relationship to senile condition. Arch. Neurol. Psychiat. 36:293–321; 1936.
130. Ryding, E. SPECT measurements of brain function in dementia; a review. Acta Neurol. Scand. Suppl. 168:54–8; 1996.
131. Sandson, T. A.; Price, B. H. Diagnostic testing and dementia. Neurol. Clin. 14:45–59; 1996.

132. Sano, M.; Ernesto, C.; Thomas, R. G.; Klauber, M. R.; Schafer, K.; Grundman, M.; Woodbury, P.; Growdon, J.; Cotman, C. W.; Pfeiffer, E.; Schneider, L. S.; Thal, L. J. A controlled trial of selegiline, α-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study [see comments]. N. Engl. J. Med. 336:1216–22; 1997.
133. Schellenberg, G. D. Progress in Alzheimer's disease genetics. Curr. Opin. Neurol. 8:262–7; 1995.
134. Schneider, R.; Wieczorek, V. Historical aspects of neurosciences. Otto Binswanger (1852–1929). J. Neurol. Sci. 103:61–4; 1991.
135. Schorer. Historical essay: Kraepelin's description of Alzheimer's disease. Int. J. Aging Human Dev. 21:235–238; 1985.
136. Schottky, J. Uber präsenile Verblödungen. Z. ges. Neurol. Psychiat. 140:333–397; 1932.
137. Seeman, T. E.; Berkman, L. F.; Charpentier, P. A.; Blazer, D. G.; Albert, M. S.; Tinetti, M. E. Behavioral and psychosocial predictors of physical performance: MacArthur studies of successful aging. J. Gerontol. A. Biol. Sci. Med. Sci. 50:M177–83; 1995.
138. Selkoe, D. J. Alzheimer's disease: A central role for amyloid [see comments]. J. Neuropathol. Exp. Neurol. 53:438–47; 1994.
139. Selkoe, D. J. Amyloid β-protein and the genetics of Alzheimer's disease. J. Biol. Chem. 271:18295–8; 1996.
140. Shakespeare, W. Hamlet. In: Harbage, A., ed. William Shakespeare—The Complete Works. New York: Viking Penguin; 1977: 1107–1135.
141. Sheng, J. G.; Ito, K.; Skinner, R. D.; Mrak, R. E.; Rovnaghi, C. R.; Van, E. L.; Griffin, W. S. In vivo and in vitro evidence supporting a role for the inflammatory cytokine IL-1 as a driving force in Alzheimer pathogenesis. Neurobiol. Aging 17:761–6; 1996.
142. Simchowicz, T. Histologische Studien über die senile Demenz. Hist. histopath. Arb. 4:267–444; 1910.
143. Simonian, N. A.; Coyle, J. T. Oxidative stress in neurodegenerative diseases. Annu. Rev. Pharmacol. Toxicol. 36:83–106; 1996.
144. Singer, C. A Short History of Medicine. New York: Oxford University Press; 1928.
145. Small, G. W. Neuroimaging and genetic assessment for early diagnosis of Alzheimer's disease. J. Clin. Psychiatry. 14:9–13; 1996.
146. Smith, A. D.; Jobst, K. A. Use of structural imaging to study the progression of Alzheimer's disease. Br. Med. Bull. 52:575–86; 1996.
147. Smith, C. D. Quantitative computed tomography and magnetic resonance imaging in aging and Alzheimer's disease. A review. J. Neuroimaging 6:44–53; 1996.
148. Smith, M. A.; Sayre, L. M.; Monnier, V. M.; Perry, G. Radical AGEing in Alzheimer's disease [see comments]. Trends Neurosci. 18:172–6; 1995.
149. Summers, W. K.; Tachiki, K. H.; Kling, A. Tacrine in the treatment of Alzheimer's disease. A clinical update and recent pharmacologic studies. Eur. Neurol. 3:28–32; 1989.
150. Terry, R., D.; Gonatas, N. K.; Weiss, M. Ultrastructural studies in Alzheimer's presenile dementia. Am. J. Pathol. 44:269–281; 1964.
151. Terry, R. D. The fine structure of neurofibrillary tangles in Alzheimer's disease. J. Neuropath. Exp. Neurol. 22:629–642; 1963.
152. Terry, R. D. The pathogenesis of Alzheimer disease: An alternative to the amyloid hypothesis. J. Neuropathol. Exp. Neurol. 55:1023–5; 1996.
153. Torack, R. The early history of senile dementia. In: Reisberg, B., eds. Alzheimer's Disease. New York: The Free Press; 1983:23–28.
154. Torack, R. M.; The Pathologic Physiology of Dementia. New York: Springer-Verlag; 1978.
155. Trojanowski, J. Q.; Lee, V. M. Phosphorylation of paired helical filament tau in Alzheimer's disease neurofibrillary lesions: Focusing on phosphatases. FASEB J. 9:1570–6; 1995.
156. Trojanowski, J. Q.; Shin, R. W.; Schmidt, M. L.; Lee, V. M. Relationship between plaques, tangles, and dystrophic processes in Alzheimer's disease. Neurobiol. Aging 16:335–40; discussion 341–5; 1995.
157. van Braunmühl, A. Neue Gesichtspunkte zum Problem der senilen Plaques. Z ges. Neurol. Psychiat. 133:391–441; 1931.
158. van Swieten, J. C.; Caplan, L. R. Binswanger's disease. Adv. Neurol. 62:193–211; 1993.
159. Venzmer, G. 5000 Years of Medicine. New York: Taplinger Publishing Co., Inc; 1968.
160. Wahlund, L. O. Biological markers and diagnostic investigations in Alzheimer's disease. Acta Neurol. Scand. Suppl. 165:85–91; 1996.
161. Wahlund, L. O. Magnetic resonance imaging and computed tomography in Alzheimer's disease. Acta Neurol. Scand. Suppl. 168:50–3; 1996.
162. Walford, R. L. The role of autoimmune phenomena in the ageing process. Symp. Soc. Exp. Biol. 21:351–73; 1967.
163. Wallin, A.; Blennow, K. Clinical subgroups of the Alzheimer syndrome. Acta Neurol. Scand. Suppl. 165:51–7; 1996.
164. Wilkins, R. H.; Brody, I. A. Alzheimer's disease. Arch. Neurol. 21:109–10; 1969.
165. Wilks, S. Clinical notes on atrophy of the brain. J. Ment. Sci. 10:10–19; 1864.
166. Willis, T. Practice of Physick (1684). In: Hunter, R.; Macalpaine, I., eds. Three Hundred Years of Psychiatry (1535–1860): A history presented in selected English texts. Hartsdale, New York: Carlisle Publishing; 1982:189–192.
167. Wisniewski, H. M.; Wegiel, J.; Kotula, L. Review. David Oppenheimer Memorial Lecture 1995: Some neuropathological aspects of Alzheimer's disease and its relevance to other disciplines. Neuropathol. Appl. Neurobiol. 22:3–11; 1996.
168. Wisniewski, T.; Frangione, B. Molecular biology of brain aging and neurodegenerative disorders. Acta Neurobiol. Exp. (Warsz.) 56:267–79; 1996.
169. Xanthakos, S.; Krishnan, K. R.; Kim, D. M.; Charles, H. C. Magnetic resonance imaging of Alzheimer's disease. Prog. Neuropsychopharmacol Biol. Psychiatry 20:597–626; 1996.
170. Yen, S. H.; Liu, W. K.; Hall, F. L.; Yan, S. D.; Stern, D.; Dickson, D. W. Alzheimer neurofibrillary lesions: Molecular nature and potential roles of different components. Neurobiol. Aging 16:381–7; 1995.