

ALZHEIMER'S DISEASE (SENIUM PRÆCOX): THE
REPORT OF A CASE AND REVIEW OF
PUBLISHED CASES

BY SOLOMON C. FULLER, M.D.

*(From the Pathological Laboratory, Westborough State Hospital,
Westborough, Mass.)*

The first published case presenting the combination of clinical symptoms and microscopical changes discussed in this paper was reported by Alzheimer (1) in 1906. Since then similar observations have been recorded by Bonfiglio (2), Sarteschi (3), Perusini (4), Barrett (5), Alzheimer (6), Bielschowsky (7), Lafora (8), Fuller (9), Betts (10), Schnitzler (11), and Jansens (14).

The case described here is included as an example of Alzheimer's disease in the report on a group of 93 brains examined with reference to origin, diagnostic significance and finer structure of so-called senile or Fischer's plaques. Owing to the variety of psychoses in the earlier communication, the large number of clinical abstracts and the abbreviated manner in which the case was presented, a further report is undertaken. The chief reason, however, for this elaboration and the review of all published cases known to the writer, is furnished by the lively interest shown in the type of mental disorder to which Alzheimer was the first to call attention. The cases from the literature are given below in chronological order, the clinical abstracts in full, and the anatomical findings summarized in the discussion.

While more or less definite mental symptoms and structural alterations are referred to in this paper, the recorded cases are too few—even these showing important variations—to warrant maintaining anything comparable to the paradigm of general paresis. The earlier reports, along with other details mentioned in their microscopical descriptions, emphasize the combination of miliary plaques with a certain basket-like appearance of ganglion cells occasioned by a peculiar alteration of intracellular neurofibrils. But within the present year¹ Alzheimer himself has

¹ 1911.

published a case in which numerous large miliary plaques of the brain were a striking feature, but in which no ganglion cell exhibited the peculiar type of alteration. (*Vide infra* Alzheimer's second case.) The last recorded observations (Schnitzler's case) note the Alzheimer degeneration of ganglion cells, but not a single plaque was found in the many areas of the brain examined. The busy delirium, excitement and confusion which have characterized the clinical course of some of the cases have been wanting in others, their place being taken by an apathetic dementia. The aphasic symptoms and ideational apraxia have also failed in some of the cases. Nevertheless, when this has been said, it must also be said that the clinical and anatomical findings offer a striking similarity. Although the total number of cases is small upon which the conception of this type of mental disorder is based, the assumption of a clinical type or subgroup is not altogether unwarranted. These cases clearly indicate that psychoses occurring in or about the period of senium are a rich field for clinical and anatomical research. The Westborough case is presented as cumulative data toward the isolation of a type which while lacking at present some of the postulates of a disease entity, may yet crystallize into such.

W. S. H., No. 9,378, a man 56 years of age, for some time previous to his final breakdown (about 2 years) had shown a memory defect, short periods of apparent unconsciousness or dream-like states, verbal amnesia and occasional paraphasia, but had been able to continue at work as a laborer on a farm where he had been employed for many years. His sister states that the memory defect had been gradual, and while at first the short periods of confusion (of a few minutes duration), in which he spoke in a paraphasic or senseless manner, were only seldom observed, of late these had become very frequent. Recently, even when there was no apparent mental confusion, he often seemed unable to find the proper word or words to employ in ordinary conversation. He would often search for things which lay directly before him and would use familiar objects incorrectly, (apraxia). Within the last 6 months when he had visited his sister's home, he would relate to her over and over again the same experience within the course of a few minutes, apparently forgetting that he had already done so. On going to bed he would make separate bundles of his clothing, placing one here, another there, in out of the way places, and in the morning could not remember what he had done with his things.

Twenty years ago he had separated from his wife on account

of her infidelity. This affair had worried him quite a little, but he formerly never spoke of it to any one. Of late, however, he constantly referred to his wife in conversation, wondered where she was and whether he had done the proper thing in leaving her. As a result he was slightly depressed. It appears that his wife was certainly at fault while he has always borne a reputation for integrity and industry. He was the father of three children by this union, one of which died in infancy from cerebrospinal meningitis, the others now of age and in good physical and mental health.

About 10 days prior to admission to hospital he had a "mild" attack of influenza with which marked mental symptoms were associated. During this attack he had been very restless, particularly at night, roamed about the house, talked much about his work and went through movements as though employed at his usual daily tasks. Finally he began to tear the bed-clothing, was manifestly disoriented and confused, apparently forgot movements employed in dressing and feeding himself and lost control of bladder and rectal function, or at least performed these latter functions without regard to ordinary rules of decency and tidiness.

The mother of patient died of apoplexy at the age of 61, father at about 65 from an affection of the stomach. No other family history of importance elicited.

On admission to Westborough State Hospital, Jan. 27, 1911, he was in a fairly well nourished condition but looked older than his stated age (56) and presented in his person the appearance of neglect. The gait was rather unsteady but not characteristic of anything more than a general weakness combined with what appeared to be a senile trepidancy; no evidence of paralysis detected. A systolic murmur, best heard at the apex, a full and rapid but regular pulse, firm radial and temporal arteries were present. Respiratory movements were of the costal type, broncho-vesicular breathing and a few râles on right side.

The pupils were slightly irregular in outline but of equal diameter, reacting sluggishly to light, the right more sluggishly than the left. Accommodation tests unsatisfactory owing to lack of proper coöperation. Acuity of vision could not be determined. The patient also failed to coöperate in tests for hearing and for the same reason integrity, or the extent of impairment, of taste, olfactory and tactile sensibility could not be definitely determined. As noted above there were no paralyses, no contractures. Muscular development was fair but rather flabby. Coördination tests were poorly executed; no Romberg; tendon reflexes increased. No history of lues or cerebral insult was obtained. He had used alcohol moderately.

When first seen by examining physician he was very somnolent and could be aroused only with difficulty. Mentally he

was not only dull but apparently indifferent, was disoriented for time, place and persons and was without grasp on his surroundings. Speech reactions were slow, indistinct—often degenerating into a scarcely audible jargon—data frequently incorrect. There was often a logoclonic repetition of the last word of a sentence or last syllable of a word and with fatigue, easily evoked, he became paraphasic. Memory defect was marked for the grossest events of his life, the recent as well as the remote.

Q. What is your name? A. Charles E. G.— +

Q. What is your age? A. Charles E. G.—.

Q. What is your age? A. Fifty-ty-ty.

Q. How old are you? A. Fifty-six. +

Q. Where were you born? A. Unintelligible muttering, then finally, Watertown.

Q. Where is your home? A. My home was born in Boston I suppose by my mother and her name was Stagpole. (Maiden name of mother was Stackpole.)

Q. Where is your home? A. I have no home but hopple popple home all the time.

Q. Where are you now? A. I know I am from another room as where from another room.

Q. What kind of a place is this? A. Kind of a wooded play. Etc.

He was able to name and indicate the use of objects shown him—pencil, knife, keys, watch.

When given pencil and paper and directed to write his name and address, he grasped the pencil in a proper manner, placed the paper on a hard surface and laboriously made a few marks but did not form a single letter. Questioned whether or not the marks were intended for his name he replied "yes." Repeated attempts were equally futile.

Jan. 28, 1911, the day following admission, he was a little brighter mentally and for a while during the interview with examiners he answered questions readily and in an orderly manner, but he was still disoriented. He could not tell how long in hospital, the nature of the institution, or remember that he had seen one of the examiners on the evening previous. He showed no concern when informed as to the character of the hospital. "Garfield is president" and he had "never heard of Roosevelt." He did not remember how long his wife had been dead (death of wife 2 years ago¹), at first maintaining that she was still alive. During the interview he frequently exhibited a verbal amnesia and was occasionally paraphasic. He could name objects shown him—bed-room furniture and small articles such as are carried on the person—and execute simple commands but easily became confused with more complex tests, such as: 3 pieces of paper of different sizes of which he was directed to

¹ Statement of patient (incorrect).

tear up the largest, give the middle sized one to examiner and put the other in the pocket of his bath robe. Go to the window, knock on the pane, come back and sit down, etc.

Feb. 3, 1911. Following the last note he was very noisy and restless at night; frequently confused and destroyed the bed-clothing.

Feb. 7, 1911. Rapid physical and mental failure; very unsteady on feet; for the 2 days previous he had failed to respond to all questions; remained in bed, constantly disturbing the bed-clothing or moving his arms about in a purposeless manner. Frequent unintelligible mutterings; extremely resistive.

Feb. 8, 1911. Pronounced clonic spasms of the left shoulder; clouding of consciousness; labored breathing; difficulty in swallowing; extreme resistance.

Feb. 9, 1911. Death with symptoms of bronchopneumonia. Autopsy 16 hours post mortem.

Anatomical Diagnosis.—Chronic external pachymeningitis, hernia of Pacchionian granulations through the dura, chronic hypertrophic leptomenigitis, pial congestion and moderate pial edema, advanced cerebral arteriosclerosis, regional atrophies of cerebrum (frontal right and left, and temporal left); chronic endocarditis; bronchopneumonia; chronic perihepatitis; chronic perisplenitis; moderate chronic interstitial nephritis.

The brain with pia attached and before sectioning weighed 1,445.8 grams. While within the accepted range of normal weights, focal cerebral atrophies were displayed in the frontal regions and in the left temporo-sphenoidal lobe, atrophies not accounted for by previous hemorrhage, softening gumma or new growth. Section of cerebrum, pons, medulla and cerebellum were negative for coarse focal lesions other than the atrophies mentioned. The larger vessels of the base and many branches of the mesial and convex surfaces of the cerebrum were sclerotic, tortuous and did not collapse on section, besides exhibiting atheromatous patches which imparted a beaded effect. The lining of the ventricles was smooth, the ventricular capacity within normal range, cysts of choroid plexus. The spinal pia was slightly clouded and presented several small osteomata occurring chiefly in the ventral portion of the thoracic distribution of the membrane. The cord shared in the general congestion, other than this offering no gross lesions. The microscopical examination revealed the following:

Mesoblastic Apparatus.—The pia in alcohol-fixed sections stained with toluidin (frontal, precentral, temporal and calcarine regions) shows that the thickening noted macroscopically is due chiefly to a proliferation of connective tissue fibers and fibroblasts, presenting a meshed appearance in which are cells of variable size containing lipoid granules (*Abraumzellen*). The frontal pia presents the greatest number of such cells though

they are by no means scant in the other areas examined. Not infrequently they are found in great numbers in the portion of the membrane immediately adjacent to the cerebrum, but disposed in a single layer which extends for some distance. Infiltrative phenomena, save for an occasional mast cell, fail completely. Hemorrhages of variable size, though never large, are present chiefly in the frontal distribution of the pia; and clear spaces within the thickened membrane, sometimes beneath and lifting the membrane from the cerebrum, are also seen, the result, in all probability, of the edema noted macroscopically. Practically all pial vessels show a proliferation of the adventitia and proliferative as well as regressive alterations of the endothelium, the latter shown by a rich lipid content of the protoplasm of cells. The blood vessels of the cortex rather generally, but particularly in the frontal areas, are increased, packets and evidence of budding are common and in low power views the richness of the vascular apparatus is at once striking. With high magnifications, aside from the progressive-regressive phenomena in vessels of larger caliber, one encounters large cells with a rich lipid content of the same general character as those noted in the pia. Such cells are found in the perivascular spaces as well as within the adventitia. There is scarcely a blood vessel in which the protoplasm of endothelial cells is not plainly visible and in which such cells do not show a pigmentation of their protoplasm. In toluidin specimens the pigment or lipid content mentioned is either unstained, presenting then its natural yellow color or is tinged a greenish or bluish yellow. But in frozen sections stained with scarlet after Herxheimer, these lipid granules are colored a bright red and because of a like appearance in the majority of ganglion and glia cells, are the most characteristic elements in sections so treated. Occasionally a small cortical vessel presents the appearance of a hyaline degeneration. As in the pia the vessels of the cortex and marrow are without infiltrative phenomena save for an occasional mast cell, and of these not more than a half dozen are encountered in all of the sections mustered.

Glia.—The stellate cells of the molecular layer are increased in number, many showing fairly distinct processes and comparatively abundant protoplasm, even in alcohol sections stained with toluidin blue after Nissl. Their general form, however, is better displayed with Mann's eosin-methylene blue solution, Mallory's phosphomolybdic, Van Gieson's stain after bichromate fixative and also quite well by Bielschowsky's silver aldehyde method, while their lipid content is best shown by Herxheimer's method. Rod-shaped cells (*Stäbchenzellen*) are quite frequently encountered, particularly in the three outer cortical laminae but these appear to be of glial origin, not a few of the so-called trabant or satellite cells being of this form. Colonies of proliferating glial

cells, mostly small elements, are seen throughout all the cortical laminæ and in the marrow, but most numerous in the molecular layer and white substance. Glial nuclei are rather generally increased. Cellular gliosis, particularly in the neighborhood of

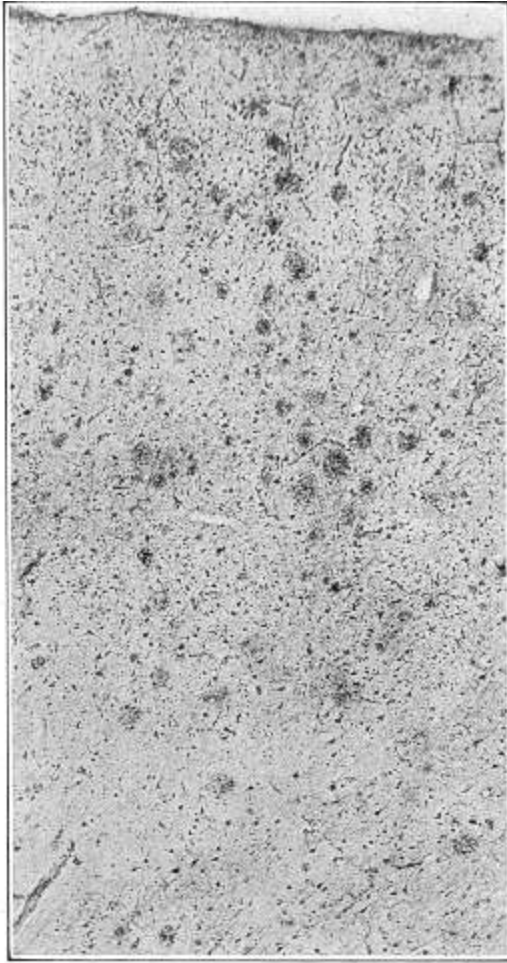


FIG. 1. Right prefrontal cortex showing a rich deposit of plaques.

many blood vessels, is shown by all cell methods, and with Weigert glia fiber stain, also with Mann's stain, a glial fibrillosis in excess of the normal is demonstrated. A striking feature is the absence of any particularly marked satellitosis, indeed, about

many cells showing most advanced degeneration of the Alzheimer type satellites are often wanting. Giant glia cells of the Deiters' variety are conspicuous by their extreme paucity, even in the white substance. The glia "keel" in Weigert preparations



FIG. 2. Left Ammon's horn. More than a hundred plaques may be counted.

is increased in extent and a richer fibrillosis than usual is shown.

Nervous Elements.—Low magnifications of sections stained with toluidin blue, particularly in the prefrontal areas, to a less degree in the other areas examined, reveal a disappearance of ganglion cells, following no definite plan, although perhaps most

pronounced among the smaller pyramidal cells. With the oil immersion, striking features are extreme fuscous degeneration of ganglion cells, not confined to the basilar portion but distributed in many instances throughout the protoplasm including

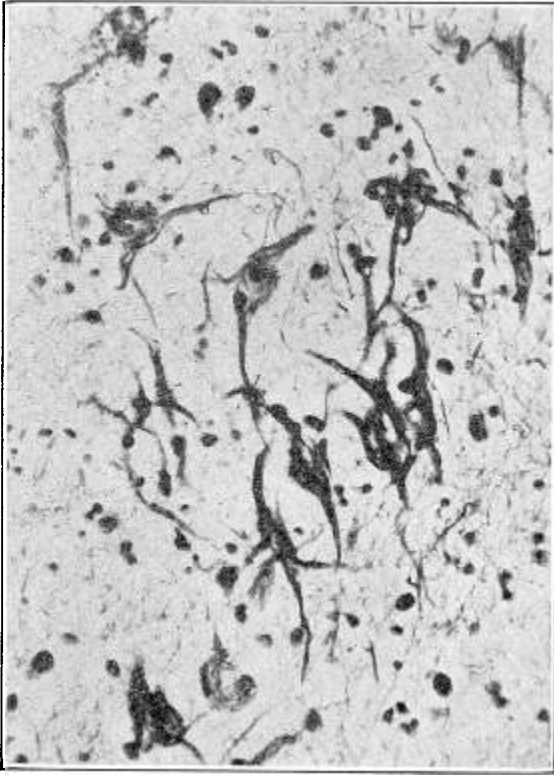


FIG. 3. Island in plexiform layer of left gyrus hippocampi. All ganglion cells showing Alzheimer degeneration.

such processes as are visible, large vacuoles in cells, atrophic cells, incrustations, extreme tortuosity of apical dendrites and shadow forms. Striking exceptions are the Betz cells of the paracentral lobule and anterior central cortex which for the most part exhibit a fair preservation. The fat content (lipoid substances) of the altered ganglion cells is best shown in Herxheimer sections, in many cells beautifully displayed in the dendrites. With the Bielschowsky silver impregnation method, easily the most characteristic findings are the presence of a great number of plaques of variable size and numerous ganglion cells exhibiting a basket-like alteration—Alzheimer degeneration.

The plaques are also well demonstrated with Mann's solution, fuchsin light-green stain, Van Gieson, though indifferently, toluidin blue on frozen sections, and negatives of them are seen in sections stained by the Wolters-Kultschitzky method for myelin sheaths. With Herxheimer's stain on frozen sections—a

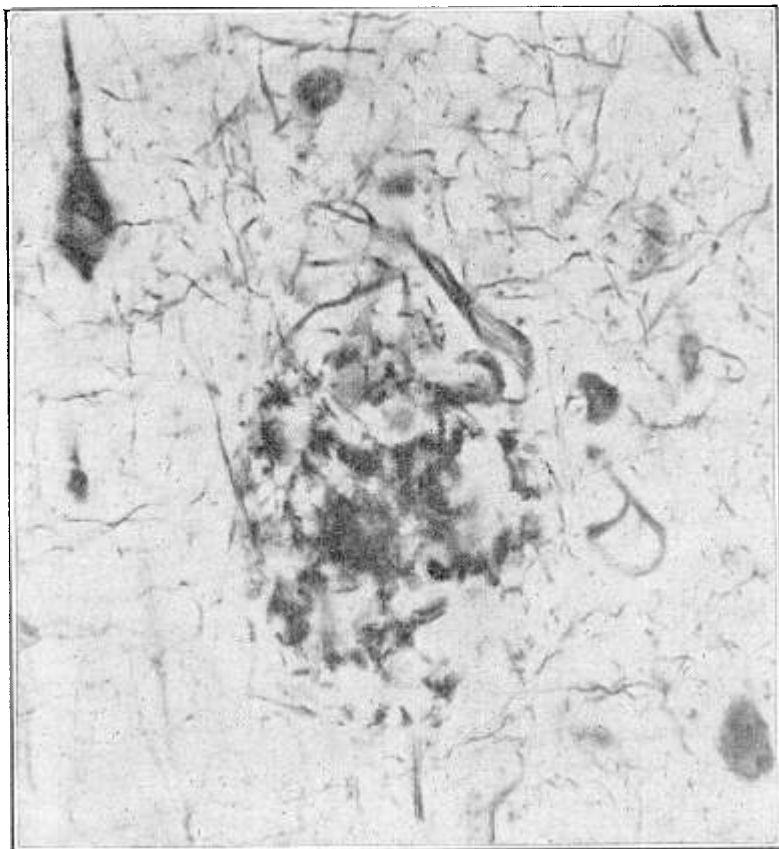


FIG. 4. Typical plaque. Alzheimer degeneration also shown.

method in my hands usually unsuccessful for plaques—not a few of these structures were displayed, the whole plaque stippled throughout with fine red granules, paler and smaller than the lipid granules in ganglion and glia cells and in cells of the vascular wall already noted. The plaques are distributed without special reference to cortical stratigraphy and are also seen in good number in the marrow stalk of gyri. The greatest richness was exhibited in the frontal, left temporal and hippocampal areas.

These structures were also found in the basal ganglia (lenticular nucleus, thalamus), in the brain stem and in the medulla. In the cerebellum no typical plaques are found but not infrequently with the Bielschowsky method, toluidin blue and in sections stained with Mann's solution, single amyloid bodies or groups of such

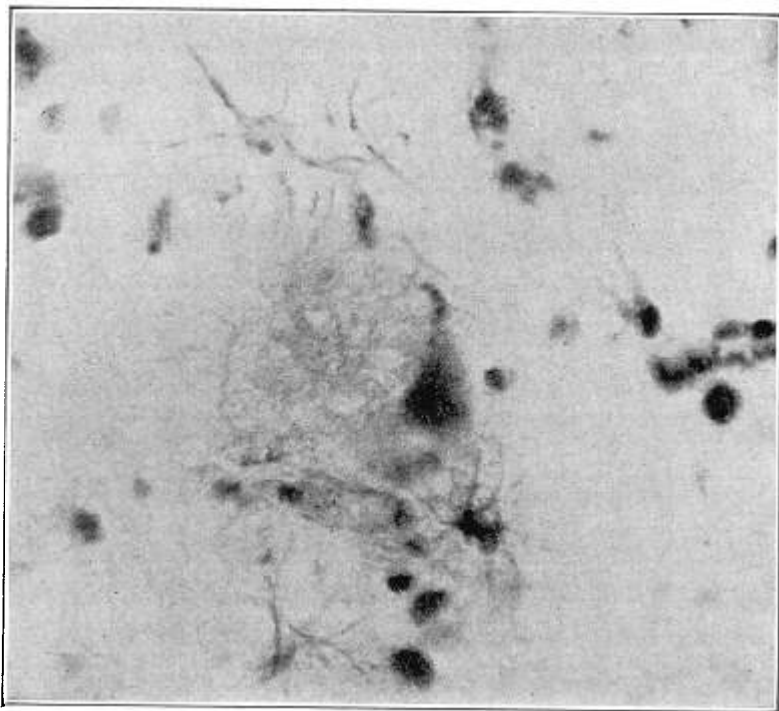


FIG. 5. Glia fibres penetrating plaque. Weigert glia stain.

are found in many foliæ, usually in the molecular, rarely in the granular, layer and white substance, around which a reactive cellular and fibrillary gliosis of a mild degree is shown. In general the number and distribution of plaques correspond with the distribution and intensity of general histological alterations. Since these latter are generally diffused through the brain plaques are also diffused. Recent and old plaques are present, differentiated by glial reactions in their vicinity, and of the same character as I have described elsewhere (9). Very small plaques not much greater in diameter than a large lymphocyte of the blood stream and plaques nearly equalling in diameter the depth

of a cortical lamina were found, and between these extremes all sizes. The rosette form and the radiary actinomycotic shapes were present as well as mixtures of these types, their finer composition such as I have described elsewhere (9).

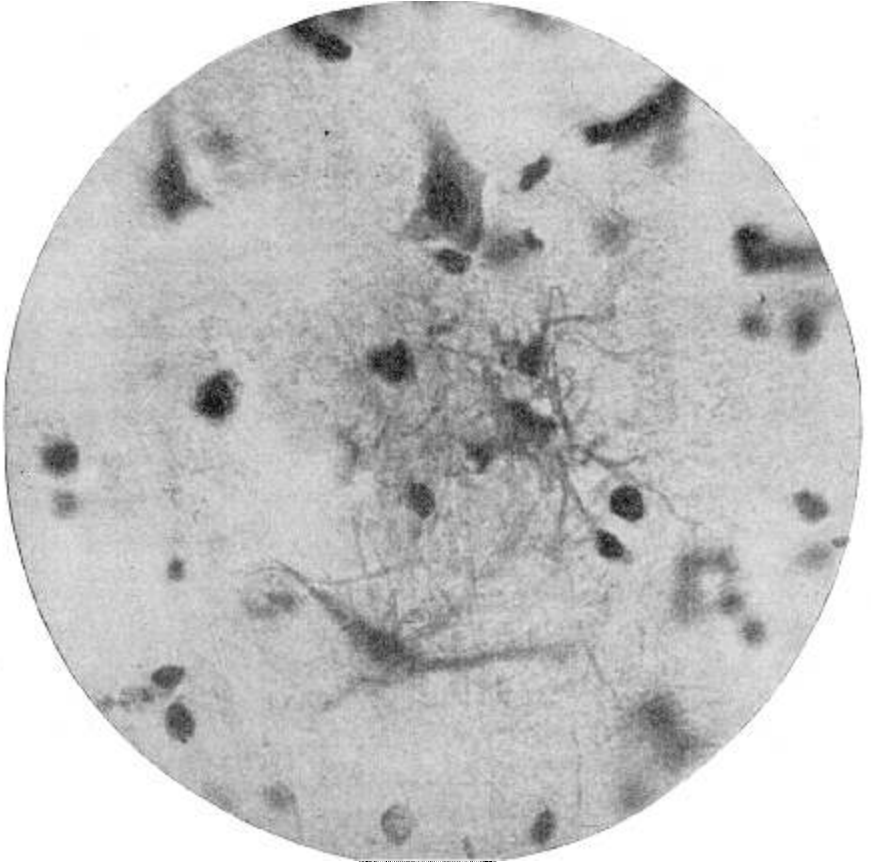


FIG. 5a. Beginning glia encapsulation of plaque. Weigert glia stain.

Many ganglion cells, fully two thirds of those in the frontal sections, all of the ganglion cells in the islands of the plexiform layer of the hippocampal gyri, all of the large pyramidals of Ammon's horn, exhibit the Alzheimer type of degeneration. This degeneration consists of a tangled mass of thick, darkly staining snarls and whirls of the intracellular fibrils, evidences of which are also shown in sections treated with Mann's solution. One sees occasionally in preparations where Alzheimer degenerations are demonstrated, finer fibrils more of the character of normal fibrils which appear to emerge from the thick bundles. Such

pictures suggest the possibility, as Bielschowsky points out, of an incrustation of neurofibrils with foreign stuffs of pathological metabolic origin. Alzheimer had interpreted these coarse fibrils as the result of a welding together of degenerated neurofibrils which had undergone a chemical alteration, staining by other methods not ordinarily displaying neurofibrils. Fischer speaks of these intracellular alterations as coarse-fibered proliferation of the neurofibrils of ganglion cells (*grobfaserige Fibrillenwucherung der Ganglienzellen*).

Résumé.—While data concerning the early history of the case is meager, this may be said: a man of 56 began to show mental symptoms at the age of 54. These were, defective memory, speech disturbances of a sensory character, transitory periods of confusion and a gradually progressive mental weakening, culminating during an attack of influenza in marked mental confusion, ideational apraxia and untidiness in the passage of urine and feces. During a hospital residence of 12 days, somnolency alternating with periods of busy delirium, excitement and speech disturbances of a sensory character, were observed, at the end clonic spasms of shoulder muscles, clouding of consciousness and bronchopneumonia. Unfortunately a Wassermann or Noguchi test was not made, but the later anatomical findings did not indicate previous luetic infection.

At autopsy, regional cerebral atrophies and arteriosclerosis of larger vessels were noted. Microscopically, vessel proliferation, progressive-regressive changes in vessel walls but no infiltrative phenomena, cortical devastations, atrophic and richly pigmented ganglion cells and the presence of so-called Alzheimer degeneration in many such cells, cellular and fibrillary gliosis, the former mostly of small elements, the latter chiefly of delicate caliber, were seen and also numerous miliary plaques in all areas of the cortex, basal ganglia, brain stem and medulla, and marked Alzheimer degeneration. No evidence of cerebral lues or general paresis was present. In short, a clinical and anatomical picture in many respects not unlike the severest form of senile dementia and yet in other ways quite distinctive. The writer considers the case one of Alzheimer's disease (*senium præcox*) and its similarity to other published observations may be seen in the following cases from the literature:

I

(Alzheimer's first case, also reported as Perusini's Case I, translated from Alzheimer's originally published notes, l. c.)

A woman, 51 years of age, presented as the first most striking mental symptom, ideas of jealousy concerning her husband. Soon after, a rapidly developing mental weakening was noticed; she would lose her way about in her own home, throw things around and hide herself for fear of being killed.

In hospital she seemed perplexed, was disoriented for time and place, occasionally complained that she understood nothing and of an inability to express her thoughts. She frequently greeted the physician as a social caller, making excuses meanwhile that her housework was still unfinished. At other times she would cry out in fear thinking that the physician would cut her or evidence distrust of him, believing that her honor would be assailed. At times she was delirious; tossed the bed-clothing about, called out for her husband and daughter and appeared to have auditory hallucinations. Frequently she shouted loudly for hours at a time.

Whenever she was unable to mentally grasp a situation she would cry out loudly, this, too, whenever an examination was attempted. Only through repeated and patient effort was anything finally obtained from her. Retention (*Merkfähigkeit*) was markedly impaired. When shown objects she named them for the most part correctly, but immediately forgot them. In reading she went from line to line spelling out the words or read without inflection. In writing she repeated many syllables, left out others, but executed the tests rapidly. In speaking she misplaced words—occasional paraphasia—and perseveration was frequent. Many questions asked her were apparently not understood. The gait was undisturbed and use of the hands was equally good. Patellar reflexes were present; the radial arteries firm; no increase in the area of cardiac dullness; no albumin in the urine.

In the further course of the disease the focal symptoms were sometimes more pronounced, sometimes less so, but throughout never intense. The patient finally was completely demented; confined to bed with contractures of the lower extremities; and passed urine and feces involuntarily. In spite of greatest care decubitus developed. Death after a duration of $4\frac{1}{2}$ years.

The autopsy revealed a diffusely atrophied brain without macroscopic focal lesions, the larger cerebral arteries sclerotic.

In sections handled after the Bielschowsky silver impregnation method a striking alteration of the neurofibrils was shown. In an otherwise seemingly normal cell there appears at first one or more fibrils which on account of increased thickness and increased tingibility stand out prominently. In the further course of the alteration many neighboring fibrils are similarly affected. These, then, form thick bundles which gradually come to the surface of the cell. Finally the nucleus and cell disintegrate and only a tangled bundle of fibrils remains to indicate the site of a former ganglion cell.

That these fibrils are colored by other staining methods which do not display neurofibrils indicates a chemical alteration in the fibril substance. This can well be, for the fibrils survive the destruction of the cell. The alterations in the neurofibrils appear

to go hand in hand with a deposition of not yet definitely determined pathological metabolic stuffs. About $\frac{1}{4}$ to $\frac{1}{3}$ of all ganglion cells of the cerebral cortex exhibited this peculiar alteration of the fibrils. Many ganglion cells, particularly in the upper cell laminæ, had disappeared.

Throughout the entire cortex, especially numerous in the outer layers, were found many miliary foci, the result of a deposition of peculiar stuffs in the brain substance. These foci may be recognized without staining, but are very refractory to staining methods.

There was a rich proliferation of glia fibers and many glia cells exhibited large fat sacs. There was no infiltration of the walls of vessels, but proliferative changes of the endothelium were demonstrable and occasionally vessel proliferation was encountered.

II

(Bonfiglio's case, also reported as Perusini's Case IV, translated from the German of Perusini (4).)

Schl. L., a judge's secretary, 63 years old.

A brother was insane. In early life the patient had been a heavy drinker. He had had gonorrhœa; in 1870 syphilitic infection and since 1872 had suffered from a spinal affection—sensation of numbness and heaviness in the legs, occasional involuntary passage of urine.

In 1902 he went to hospital on account of his spinal trouble. At that time he looked older than his reported age; the skin of the face and neck was a light grayish blue color (had been treated for a long time with silver nitrate); right pupil larger than the left, pupillary reflexes intact; an old scar on the hard palate; marked disturbance of coördination of upper and lower extremities; impaired muscle sense; Romberg sign. No paresthasias were present. For the most part he was happy and elated and expressed himself in a friendly and orderly manner. Nevertheless, there was a marked memory defect. When left to himself he spoke in a loud tone, his gaze directed at the ceiling or window. He gesticulated freely, laughed and scolded occasionally and stroked his face and hair in a stereotyped manner. He would carry on imaginary conversations with his judge; hold court and condemn the fancied prisoners to death or drive them from the court room. Often he entertained himself in imaginary social gatherings, conversing with acquaintances of his student days. He declared one person a prostitute, protested against the supposed objections of another or made protective movements against fancied threats. He believed it to be summer and that he had been already a half year in hospital. On account of his mental condition he was transferred on the following day to the psychiatric division.

To be added to the physical findings are: diminution of the

strength of the legs and diminished pain sensation in the right leg. He suffered during his residence in hospital quite a little from diarrhea; he smeared himself with feces and was almost constantly hallucinated (auditory).

June 20, 1904, he was transferred to Karthausbrüll unimproved. On admission there the patellar reflexes were noted as diminished, the pupillary reactions sluggish. He romanced freely: he was not a pensioner, an acquaintance was a bishop. He conversed continuously with voices. Marked memory defect; marked disturbance of retention. He could remember nothing of his stay in the Munich hospital, nor anything of his thirty years activity as an official of the court.

Oct. 10, 1904, the patellar reflexes could not be elicited. There were marked disturbance of equilibrium with eyes closed, increasing ataxia and marked euphoria.

March 10, 1905. A fainting attack followed a bath, but from which he quickly recovered.

Dec. 13, 1905. Increasing divergence strabismus.

March 2, 1906. Unable to walk, remains constantly in bed.

April 3, 1906. Purulent catarrhal cystitis.

Aug. 25, 1906. Chatters the day long with voices.

Dec. 31, 1906. Subnormal temperature; pulse barely perceptible.

Jan. 1, 1907. Exitus letalis.

(To be continued.)