diastolic blood pressure, the greater is the danger that the disease may take on a malignant course.

The prognosis in malignant hypertension is grave, and at the present stage of our knowledge the treatment must necessarily be symptomatic and palliative in character.


## SUMMARY

Two cases are reported with characteristic clinical and pathological findings of malignant nephrosclerosis (malignant hypertension).



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# A CASE OF ALZHEIMER'S DISEASE WITH NEUROPATHOLOGICAL FINDINGS*


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THE case which I have to present is one of Alzheimer's disease, or early senility. The condition has been studied fairly extensively, but there are certain features, both clinical and pathological, which give rise to difficulty in distinguishing it from true senility. A great deal more study will be necessary before these two conditions, which I believe to be distinctive entities, can be definitely separated. The difficulty is accentuated because there are, at first sight, certain features in the microscopic findings which are common to both, but which, on closer observation, it seems to me, do show definite differences. Clinically, the conditions can be separated by an arbitrary age limit, but such a basis does not remove the conflict which arises when the pathologist is called in. It is with the view of trying to clear up some of these difficulties that the following case is presented.

## CASE HISTORY

The patient, a female, aged 53, was admitted to hospital on August 16, 1932, with the complaints of gradually developing dementia, loss of memory, periods of restlessness, alternating with periods of depression and occasional extreme excitability.

*Family history.*—No mental or nervous disease in the family nor alcoholism or drug addiction were reported in any of the members.

*Personal history.*—As a child, the patient was bright in school, completing her high school education. She was always adjusted socially, becoming a leader in church activities and singing in the choir. She was capable of playing several musical instruments. After graduation from high school she lived at home with her mother and sister. She was very much attached to her sister, to the extent that she wished to live with her even after the sister's marriage. Although a good mixer with the female sex, she never had anything to do with the male, and there was a tendency toward a homosexual attitude.

*Medical history.*—There was nothing of note in the medical history. Alcoholism, drug addiction, venereal disease, and sexual relationship were denied. There was no record of previous nervous or mental disease prior to the onset of the present illness.

*Personality.*—The patient was reported to have been an extroverted type, jolly, clever and a good worker.

*Onset of the present illness.*—Following the death of the patient's mother, twelve years before admission, it was noted that the patient became preoccupied, on some occasions did not appear to hear conversation directed towards her, and frequently forgot matters in which she had been very punctilious. She became less careful about her house work, and occasionally would laugh foolishly. She brooded considerably over her mother's death, frequently refusing food and drink. There was a report that up to four years previous to admission, she had occasional spells when she appeared to lose consciousness, during which time she remained rigid, to such an extent that a strong person could not open her hands. She did not became blue and did not cry out, nor did she have any incontinence during these attacks, and recovered rapidly. During the four years previous to admission, these spells were not noted, but she became more forgetful, preoccupied and childish in her actions.


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She was, however, quite manageable and helped with the housework in a moderately satisfactory manner until August 5, 1932, ten days previous to admission, when she suddenly became excited for no apparent reason. She would run about the house in complete confusion, mumbling in an unintelligible manner, and laughing hysterically at times; would scream at the top of her voice for several minutes. She became abusive to her sister and brother-in-law with whom she was living, and destructive to her own clothing and articles about the house. On one occasion, she upset the dining room table with all the dishes on it. These periods would abate to some extent, but would recur, and during them she would strike anyone who came near her. She had no idea where she was or what she was doing. She was deported from the States to Fergus, Ont., where she was certified by Drs. A. Groves and F. T. Russel. She was admitted on August 16, 1932. The certificates recapitulate the foregoing history, and added that the patient had for some few days to be cared for like an infant and could not feed herself.

*Mental examination.*—When first admitted, the patient was deeply under the effects of sedatives. Shortly after admission, when the effects of the sedatives had worn off, she became restless, running about the ward and refusing to stay in bed. She was given appropriate clothing and allowed to be up. Mental examination was quite impossible due to the lack of intelligence, inability to speak, and excitability. Her conversation consisted of mumblings, and she responded with a foolish grin to questions, and occasionally by some little impulsive act such as grabbing the examiner's pen or his necktie. She offered physical resistance to being put to bed, and was content only to wander about here and there, keeping up the while a stream of mumblings interspersed with periods of foolish laughter. Following her admission, she showed no extreme excitability and there was no evidence of violence so long as she was allowed to wander about. It was impossible to state whether hallucinations or delusions were present or to estimate the power of her memory. It was the examiner's opinion that she was completely disoriented and did not know what she was doing. The examination was abandoned at this time. Further examination on November 15, 1932, gave the following impressions and information. "When one tries to enter into conversation with this patient, the most outstanding feature is the degree of dementia which is present and is very profound. It would appear as though she had no appreciation whatsoever as to what is going on, or what is being said to her. Any attempt to test her aphasia is fruitless."

The wandering was still present. She was unable to find her way back to her bed, and was apparently unconscious as to whether or not she had any clothing on, and she had to be dressed and fed. She was unclean in her habits. The expression was a fixed smile and never varied, and there was continued mumbling which was quite unintelligible. There was a slight suggestion of carrying out commands when asked to close her eyes or put out her tongue. When asked her name she gave it correctly and then continued to repeat it four or five times. When asked when she came to hospital she repeated the last word half a dozen times. This tendency to repetition was on some occasions quite marked. At this time the differential diagnosis was thought to lie between general paresis, frontal lobe tumour, arteriosclerosis, dementia præcox, senile psychosis.

It was thought, on account of the long history and absence of localizing signs that brain tumour was unlikely. The age and mental picture were thought to exclude dementia præcox. The blood Wassermann test and spinal fluid reaction were negative; there was no history of luetic infection and it was therefore ruled out. The degree of arteriosclerosis on physical examination was not extensive, and this was ruled out. The examiner states: "The diagnosis seems to rest with the early senile group, and the case is being considered as one of Alzheimer's disease".

*Physical examination.*—Weight on admission, 83 pounds. The patient looked thin and ten years older than her stated age of 53 years. Due to lack of cooperation, the examination was very unsatisfactory. It was noted, however, from fleeting glimpses of the eye grounds, that they were pale but sharply defined, and it was thought that a moderate degree of arteriosclerosis was present. Nothing significant was noted about the head and neck or the chest. In the cardiovascular system, numerous extra systoles were noted; the left border of the heart extended 9 cm. left of the mid line in the 5th interspace and 3 cm. to the right in the 4th interspace; there was a slight mitral systolic murmur. The peripheral arteries were slightly palpable. The abdomen was negative. No vaginal or rectal examination was done, because of lack of cooperation.

Cranial nerves.—The first and second could not be tested; 3rd and 4th and 6th, pupils reacted to light and accommodation; the eye movements were apparently normal, but the examination was unsatisfactory. The 5th and 7th nerves appeared normal; the 8th could not be tested, but from the various partial response to commands it appeared she could hear. The 9th and 10th were negative, as was the 12th.

*Reflexes.*—The biceps, triceps, patellar and ankle jerks were equal, but slightly hyperactive. The plantar reflex was normal and there was no clonus. Coordination could not be tested. Speech could not be satisfactorily tested, but the patient sometimes repeats simple words such as King, King, King, or Peggy, Peggy, Peggy, but this is the extent of the converation.

*Sensation.*—No cooperation could be obtained, but she apparently felt pin prick throughout.

*Gait.*—The patient was weak, walked in a halting fashion, which it was thought could be accounted for by the degree of emaciation present.

At a conference of the staff on October 3, 1932, the case was diagnosed as Alzheimer's disease. On November 16, 1932, the patient was presented as a case of Alzheimer's disease at an inter-hospital conference. Considerable discussion was provoked after the diagnosis, but no other conclusion was reached.

*Progress notes.*—On December 22, 1932, the nurse in charge of this case noted a seizure which was tonic in type. The eyes were fixed, staring upwards, and the patient was frothing at the mouth. Some time following the seizure there was incontinence. The patient was receiving sedatives to control restlessness. On January 23, 1933, a further seizure was described by the nurse, occurring early in the morning, with twitching and involuntary contractions of the muscles. At this time there was incontinence during the seizure. In neither case was there any biting of the tongue. She showed some slight sign of drowsiness following the seizure, but it was not felt that the seizure was truly epileptic. On May 10, 1933, a further seizure occurred early in the morning, but with no after-effects. On July 29, 1933, a seizure of 20 minutes' duration was reported early in the morning, when she fell to the floor. Another seizure occurred on that date two hours later, which lasted for one hour, after which the patient was quite drowsy and her pupils reacted rather sluggishly to light. There were no localizing signs and no paralysis, and the seizure was thought probably due to arteriosclerotic spasm. Because of the appearance of the attacks in the early morning a hypoglycæmic epilepsy should have been considered. A similar seizure occurred August 16, 1933, and again on August 21, 1933. A note on January 10, 1934, states: "that the patient had been gradually growing weaker from day to day and died about 1 p.m. with a hypostatic pneumonia".

*Laboratory findings.*—The blood and cerebrospinal fluid gave a negative Wassermann test.

*Autopsy.*—This was performed on the date of death. The body showed extreme emaciation and looked ten years older than the stated age.

Hypostatic pneumonia in the lungs and some degree of sclerosis in the coronary arteries, and chronic sclerotic

endocarditis of both the tricuspid and mitral valves were found.

*Brain.*—The brain weighed (after fixation) 825 grams. The dura was markedly adherent to the skull cap and there was some increase of cerebrospinal fluid in the subarachnoid space. The brain itself was small, and the sulci were widened and deepened.

*Examination after fixation.*—There was extreme atrophy of the gyri throughout, but most marked in the frontal poles. The vessels at the base showed a few atheromatous plaques, but were, generally speaking, fairly well preserved. There was some thickening of the arachnoid around the base. The whole structure appeared small. The hemispheres were separated by in-

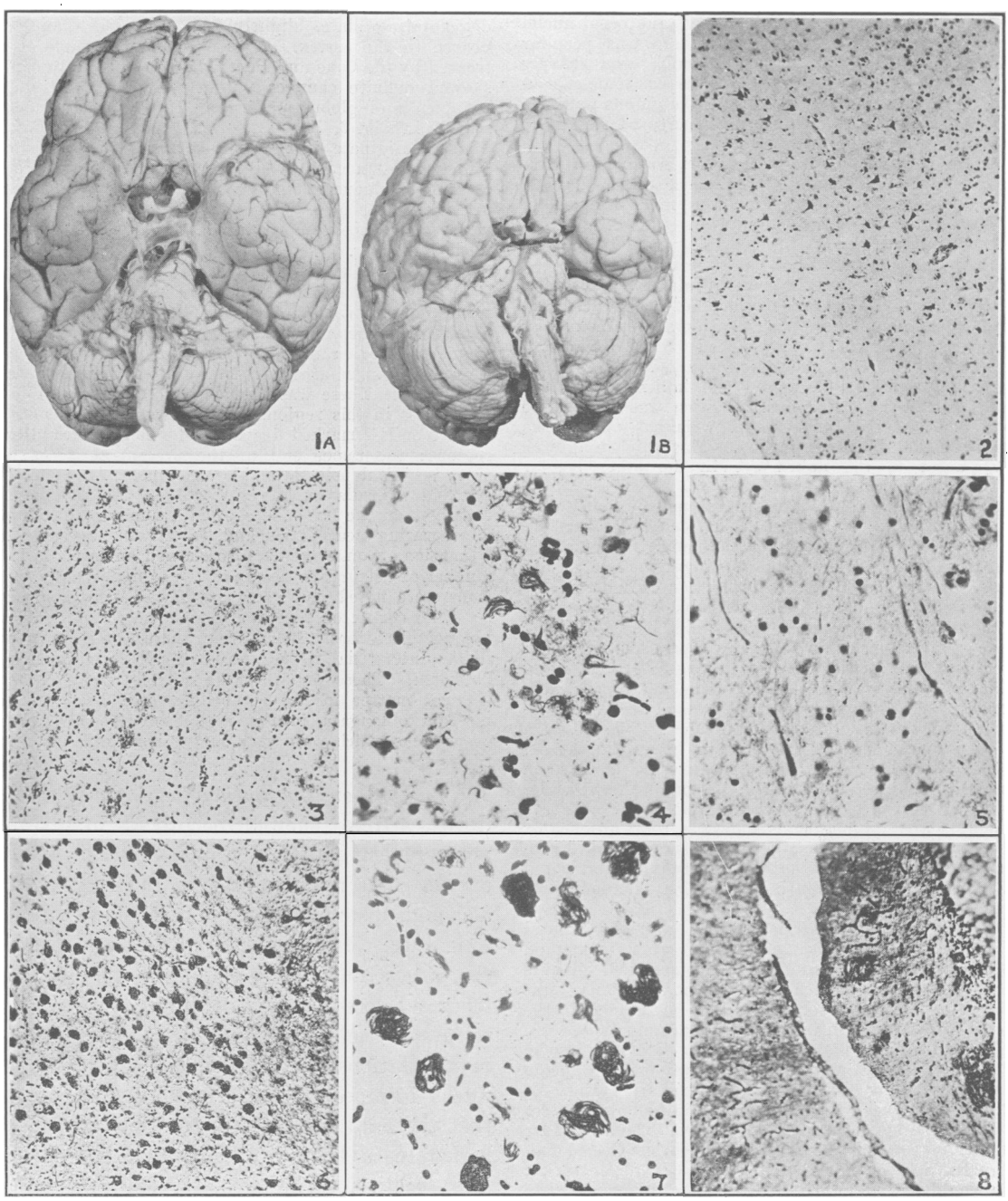


**Fig. 1A.**—Normal brain, weighing 1,230 grams, compared with **Fig. 1B,** brain from a case of Alzheimer's disease, weighing 825 grams. (Slight distortion in fixation in the brain of Alzheimer's.) **Fig. 2.**—Section of the cortex and white matter frontal pole, cresyl violet stain, showing extreme loss of nerve cells and degenerative processes in those remaining. **Fig. 3.**—L.P. Cortex frontal pole, right, Cone and Penfield's silver carbonate method, showing a large number of plaques. **Fig. 4.**—H.P. view of plaques seen in Fig. 3, showing plaques and Alzheimer's tangles. **Fig. 5.**—White matter frontal lobe, Cone and Penfield's silver carbonate method, showing secondary degeneration in neurofibrils. **Fig. 6.**—Nest of nerve cells in globus pallidus, L.P., showing tangles within the nerve cells. Note sharp limitation of the destructive process to the nerve cells. **Fig. 7.**—H.P. view of area from Fig. 6, showing tangles and early plaque formation within the nerve cells. **Fig. 8.**—Cerebellar cortex, Cone and Penfield silver carbonate method, showing plaques.

cision through the corpus callosum and brain stem. The atrophy of the gyri on the mesial surface was as marked as on the vertex. The pineal gland was cystic and calcified. The whole brain had a peculiar gelatinous appearance. The ventricles showed marked internal hydrocephalus. A transverse section was made through the right hemisphere, and showed a thinning of the corpus callosum and loss of white matter and thinning of the cortex. A further section made through the basal nuclei showed them to be shrunken, and there was peculiar streaking of the globus pallidus, which was sharply differentiated from the putamen. There was some streaking of the caudate nucleus as well as the globus pallidus, and the nuclei cut with considerable increased resistance to the knife.

Although the atrophy of the gyri was widespread, there was a marked lack of prominence of the frontal lobes, and the sulci in this region were much wider than in others. The frontal lobes were not only foreshortened, but were much thinner in a vertical direction than the normal brain. The whole structure, as indicated by the weight, was markedly reduced in size (see Fig. 1).

*Microscopic findings.*—Section of the vertebral artery, right side, showed a considerable amount of endarteritis, the lumen being reduced to half its normal size. The medial coat showed no marked changes, but there was a considerable round cell infiltration of the adventitia. The internal elastic lamina was seen to be intact, and presented the usual wrinkled appearance underneath the thickened intima. This thickening was not apparent to the naked eye in the other basilar vessels.

A section from the left frontal pole, stained with hæmatoxylin and eosin, showed some degree of thickening of the arachnoid with a slight amount of round-cell infiltration. The vessels of the meninges were somewhat engorged and at one point in the section examined there was a considerable collection of free blood in the arachnoid tissues. The cortex showed a mild increase in the surface glial tissue, the arterioles were somewhat engorged, and, very occasionally, some degree of thickening of the arteriolar wall was noted. The nerve cells were extremely rare throughout the cortex and those remaining were very degenerate in appearance. There was a relative increase in the number of interstitial nuclei noted. The white matter showed a marked increase in the number of interstitial nuclei present. Cresyl violet showed the cortex to be very thin and nerve cells are extremely scarce. Some fields showed a total absence of such cells; those which remained were pyknotic and hypochromatic in appearance, some were granular and not a normal nerve cell was seen in the section examined (see Fig. 2).

Examination of a section from the right frontal pole by the Cone and Penfield silver carbonate method showed a tremendous number of the so-called plaques (see Fig. 3). A number of compound granular corpuscles were seen throughout the cortex, and the neurofibrils were broken up and granular, and there were skein-like and basket-like forms. Under high power some of the senile plaques were seen to contain what appears to be degenerating forms of neurofibrils (see Fig. 4). Most of the plaques were seen to contain globular masses which have the appearance of cell nuclei. The remainder of the plaque was formed of granular debris. Occasionally, structures which had the appearance of degenerating fibrils could be seen lying within the plaques. The plaques were not surrounded by any process of gliosis which we could discern. There was no evidence of increase in the number of astrocytes or of glial fibres. Some of the plaques showed some degree of concentric arrangement of the granules. Some formations were noted which had the appearance of nerve cells, with granular masses which apparently represented degeneration of the intracellular neurofibrils. Only a very few normal neurofibrils were noted in any parts of the section examined.

A block from the white matter of the central portion of the right frontal pole was impregnated by the Cone and Penfield silver carbonate method, and many of the neurofibrils were seen to be swollen, granular and irregular in outline. Nothing resembling the appearance of the senile plaques as found in the cortex was noted anywhere in this section (see Fig. 5).

A section from the basilar nuclei showed a large number of corpora amylacea in the subependymal region and region of the internal capsule. Cresyl violet stain of the basil nuclei showed the nerve cells to be in a degenerating state, slightly less advanced than it appeared in the cortex. A block from the same region, treated by the Cone and Penfield silver carbonate method, showed definite changes within the nerve cells in the putamen and globus pallidus. These are well demonstrated in Fig. 6. They also offer a suggestion that the plaques originate in nerve cells, since they were completely surrounded by white matter, and the tangles and beginning plaques definitely were confined to the nest of nerve cells shown. Under the high power, these masses were seen to be composed of tangled skeins of neurofibrils (see Fig. 7).

A section taken from Broca's area, treated by the Cone and Penfield silver carbonate method, showed a tremendous number of senile plaques, some of which contained remnants of degenerating fibrils. Sections from this region stained with hæmatoxylin and eosin showed no structures which could be definitely called nerve cells. There was considerable engorgement in the capillaries in this region. These changes were noted in a more or less marked degree in the following additional regions: the upper end of the precentral gyrus right side; occipital pole, left side; region of Ammon's horn left side; insula on the right side. In addition, the thalamus on the left side showed a number of cells with degenerating neurofibrils and, in various regions, skein-formation. Some regions also showed an increase in the number of astrocytes. None of the typical plaque formations were noted, but some areas were very suggestive.

The cortex of the cerebellum showed quite definite plaque formations. In addition, there was some increase in the interstitial tissue; and rod-cell formations could be noted. These plaques were entirely confined to the cortical matter in the cerebellum (see Fig. 8). The medulla oblongata in the region of the olive showed some areas which were very suggestive of plaque formations.

*Comment on the pathological findings.*—The diffuse atrophy showed the process to have been very generalized. It would appear that this atrophy was most marked in the frontal lobes, although distortion in fixation makes it difficult to be sure. Microscopically, Broca's area showed the largest number of plaques, with the frontal lobes a close second. Clinically, mental deterioration and aphasia were early and severe manifestations. The involvement of the basal nuclei in more recent formations might suggest that the agitation and unsteadiness might have had part, at least, of their origin in lesions in this locality. The sleeplessness and loss of weight might also be linked to disturbances of vegetative functions of this area. The thalamus showed sufficient change to account for the emotional instability. From a general point of view gliosis was not a predominant feature, although localized areas were found. The wide distribution of plaques throughout the nerve cell-containing areas, and their absence in the

white matter is very suggestive of their relationship. Arteriosclerotic changes, although present in both the larger arteries and the arterioles, were no more marked than we have seen in cases showing absolutely no mental manifestations, and cannot be said to have played any very significant rôle.

## DISCUSSION

Alzheimer's disease was first described by that author[1] in 1907. Up to the present time over 90 cases have been well described in the literature. Krapf[2] has given the most extensive bibliography, and those writers of more recent date, not mentioned by Krapf, have been noted by Rothschild.[3] Numerous doubtful cases have been reported. Alzheimer's original description contains cases in the sixth decade. Perusini[4] gave a comprehensive discourse on the disease, but he also confused it with true senility, some of his cases being in the sixth decade also. Barrett[5] gave a description of 8 cases, but included some with histories starting in the seventh decade. The inclusion of cases beginning after the fifth decade of life, we feel, confuses the issue. In all probability such cases are of true senile origin, rather than the Alzheimer's reaction.

There are, however, many points of similarity between the two types, loss of memory, general dulling, memory retention disturbances, impairment of judgment, lack of initiative as compared with the individual's normal self, lack of interest in, and ability to concentrate on, matters formerly of interest, and disturbances of the affect tone, are characteristic of both conditions.

There are, however, certain clinical features which ear-mark the Alzheimer's or early type of senility. Grunthal has conveniently divided the condition into three phases.—

1. A stage of gradual loss of memory and disturbances in perception, carelessness in work and appearance, disorientation for place, weakness or epileptiform attacks, with some loss of words and slurred speech.

2. Complete disorientation for time, place, and person, dulling of comprehension, inability to read, write or do sums in simple arithmetic.

3. A stage of extreme irritability with paraphrasia, uncleanliness, and stereotyped movements.

The case we have reported showed all these stages. Most marked were the speech disturbances, rapid mental deterioration, and agitation. The early appearance of such conditions aids considerably in arriving at a conclusion. It would seem that the "youthful senile" suffers from a loss of control over a dynamic organism, while the senile shows a deterioration of the whole organism, and pursues his downward course with an accentuation of his former personality. In the first case one system is disorganized; in the second there is slowing and degeneration of the whole anatomical structure. True, the two may overlap in symptomatology, but the one is typical of energy, misdirected, especially in the early stages, while the other is exhaustion of the whole organism from the start.

Recent workers have tended toward a distinction between these groups, both from the clinical and pathological point of view. Lowenberg and Rothschild,[6] as well as other writers,[7, 8, 9] have reported cases with certain basic conditions such as syphilis, and chronic infection, and offer the suggestion that the changes found in the nervous system were secondary to either infection or toxæmia.

MacDonald Critchley *et al.*[10, 11] have attempted to distinguish microscopically, to some extent, between the plaques of Alzheimer's disease and those of true senility. Personally, we have noted that the plaques in cases of early senility and those of true or late senility have quite different appearances, those of the Alzheimer's type being much more widespread, Alzheimer's tangles are more common, and the microglial reaction is absent around the plaques. In late senility the plaques are smaller, fewer in number, and rod-cell formation around the plaque is usual. Within the limits of our experience we feel that no case having an onset after the middle "fifties" should be classified as Alzheimer's disease, unless under very exceptional circumstances. We feel also that a more thorough study of both types of cases, done under separate classifications as to age, is essential before a definite distinction can be made. Our own material is much too limited to warrant more than tentative conclusions. From what material we have seen and from the work of others we suggest that there is a distinct pathological difference between the two types of cases.

As regards the origin of the plaques, two theories have been put forward. First, that they originate from the interstitial tissue, or that they originate in nerve cells and later are added

to by the interstitial tissue. The second theory holds that they originate solely from nerve cells, and that whatever is contributed by the interstitial tissue is merely reaction to destruction of tissue and bears no relationship to the origin or formation of the plaque. In the case we have presented we have stressed the point that the plaques could only be found in those locations where nerve cells were found, and the number of plaques bore a definite direct ratio to the number of nerve cells found in any location. This we have found true, regardless of whether the case was one of early or late senile psychosis. We are therefore of the opinion that plaque formation depends entirely upon the presence of nerve-cell bodies for their formation, and that interstitial reaction is dependent upon destruction of nervous parenchyma.

## CONCLUSIONS

The case presented offers a unique history of this condition. The onset of symptoms in an otherwise normal person at the age of 41, of gradual mental deterioration with loss of memory; epileptiform seizures, not characteristic of epilepsy; early aphasia, with perservation of gradually increasing severity; periods of excitability, with aimless wanderings and disorientation, all progressing to a profound degree; and eventually unsteadiness with increasing epileptiform seizures, becoming more characteristic of epilepsy, all point to the picture of Alzheimer's disease. The total duration of the disease was twelve years, which is rather longer than usual. The pathological and microscopic findings confirm the clinical diagnosis, and are, typically, those described in the literature. So far as we have been able to learn, only two other authors have demonstrated plaques in the cerebellum, Barrett[5] in 1911, and Rothschild[3] in 1934. The appearances of the neurones in the olive were very suggestive of early plaque formations in our own case. The remainder of the central nervous system was not available for examination.

In conclusion I wish to offer my thanks to the Ontario Hospital, Hamilton, for supplying the clinical history, and allowing me to present it along with pathological studies. Dr. E. A. Linell offered some very helpful criticisms and suggestions. To Dr. Margaret S. Thompson I am grateful for her careful technical preparations, from which the photomicrographs were produced through the kindness of Dr. D. A. Irwin, Department of Medical Research, University of Toronto.

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TINNITUS.—W. J. MCNALLY *et al.* present a study of 19 cases of tinnitus, all cases of objective tinnitus being excluded, in patients of widely different ages and with different types of ear disease; most of the patients complained more of the tinnitus than of deafness. The condition may be caused by a lesion in the nerve tissue in Ménière's syndrome by intracranial disease, and possibly by otosclerosis. However, Crowe and others did not find tinnitus a prominent symptom in cases of cochlear disease, and a study of 351 patients showed that tinnitus was present in 10 per cent without obvious local ear disease. The ages of the patients in the present series ranged from 19 to 52 years, and the duration of the condition varied from a few months to thirty years. The younger patients or those who had had tinnitus for a short period did not improve as markedly under the various treatments as the older ones or those with tinnitus of longer duration. Ephedrine and bellafoline caused improvement in a greater number of cases when given orally than hypodermically. Stimulation of the sympathetic or depression of the parasympathetic nervous system was slightly more beneficial than the converse procedures. Stellate gangliectomy (depression or elimination of the sympathetic) produced improvement in 3 out of 4 cases. All measures were directed towards altering the cerebral circulation or cerebral pressure; the drugs used produced their full physiological effect, and they have been shown to act on the cerebral vascular mechanism. Despite the undoubted alteration of the cerebral circulation, the tinnitus in most cases was unaffected by the measures employed.—*J. Laryngol. & Otol.*, June, 1936, p. 363. Abs. in *Brit. M. J.*