

HISTORICAL NOTE

No Man Alone: The Rediscovery of Alois Alzheimer's Original Cases

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In 1992 and 1997, respectively, the histological slides of Alois Alzheimers original cases were rediscovered in Munich. This material, which has survived two world wars, was not originally kept at the Institute of Neuropathology of the University of Munich where it was found. Parviz Mehraein, head of the institute, saved anonymous neuropathological material given away by the Psychiatric Clinic of the University of Munich and the Max-Planck-Institute of Psychiatry. Yet it was not until Kohshiro Fujisawa of the Tokyo Metropolitan Institute of Neuroscience wrote a letter that the search leading to the rediscovery of Alzheimer's cases was initiated. Henry deF. Webster of the National Institutes of Health in Bethesda, Maryland, had mediated his contact to Munich. Histological and molecular genetic findings obtained on the tissue sections have been reported previously (Neurogenetics 1997, 1:73-80; 1998, 1:223-228). The present article summarizes the unusual history of this rediscovery and at the same time illustrates the great value of international exchange in science.

Introduction

No Man Alone is the title of a very readable book by Wilder Penfield in which he describes the foundation of the Montreal Neurological Institute (1). In his book, Penfield provides numerous examples of how personal relationships between international scientists may profoundly influence and stimulate developments at a third site. I would like to borrow the title of this book to give

credit to two well-known members of the International Society of Neuropathology, Kohshiro Fujisawa of Tokyo and Henry deE. Webster of Bethesda, Maryland (Figure 1a), whose contributions to the rediscovery of Alois Alzheimers original cases (2, 3) illustrate this principle.

Alzheimers Laboratory in Munich

From 1904 to 1912, Alois Alzheimer headed the Anatomical Laboratory of the Royal Psychiatric Hospital in Munich (4). Emil Kraepelin who had held the chair of psychiatry at Munich University since 1903 was the director of the Psychiatric Clinic and a visionary biological psychiatrist. He invited Alzheimer, Spielmeyer and later Nissl and Brodmann to his department where they built a research laboratory of high reputation. In 1912, Spielmeyer was appointed head of the Anatomical Laboratory after Alzheimer had accepted the chair of psychiatry in Breslau. As it had done under Alzheimer, the histopathological research laboratory continued to prosper and grew into a truly international center for research on brain diseases. It subsequently became part of the *Deutsche Forschungsanstalt fur Psychiatrie* (DFA) founded by Kraepelin in 1917. In 1924, the DFA joined the Kaiser-Wilhelm-Gesellschaft and in 1966 it was renamed the Max-Planck-Institute of Psychiatry. Its basic science branch including the morphological laboratories (Department of Neuromorphology) moved to the Martinsried campus in 1984 and became independent as the Max-Planck-Institute of Neurobiology in 1998.

Initiation of the search for Alzheimer's cases

The search for material from Alois Alzheimer's laboratory began with a letter I received from Henry deF. Webster (Figure 1c) dated November 5, 1992:

On my way home from Munich, I went to Toronto where the ISN Executive Committee Meeting was held. Dr. Fujisawa (an expert on aging) asked me if slides of cases Alzheimer described... are in your Institute...

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November 11, 1981

Dear Dr. Graber:

Thank you for the copy of your letter addressed to the "Senior Researcher" of the University of Toronto, dated 10/28/81, regarding the original cases of Alzheimer's disease. It is my pleasure to inform you that the original cases of Alzheimer's disease have been located and are now being reviewed by the University of Toronto.

I read the two original papers for Alzheimer's long ago, they were, in fact, the only papers I have read on the subject of Alzheimer's disease. I was struck by the fact that the original cases of Alzheimer's disease were described in a paper by Alois Alzheimer in 1907, and that the original cases of Alzheimer's disease were described in a paper by Alois Alzheimer in 1907.

As it has passed long since Alzheimer worked on these two cases in Munich and I have been busy for many years since then, I can only tell you that the original cases of Alzheimer's disease were described in a paper by Alois Alzheimer in 1907, and that the original cases of Alzheimer's disease were described in a paper by Alois Alzheimer in 1907.

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This was a great pleasure to me. I am glad to hear that you have found the original cases of Alzheimer's disease. I am glad to hear that you have found the original cases of Alzheimer's disease.

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Dr. Henry J. Graber

Henry deF. Webster, then Chief of the Laboratory of Experimental Neuropathology at the National Institutes of Health in Bethesda, Maryland, had just visited Munich where he delivered a keynote address at a Scientific Symposium organized to celebrate the 60th birthday of Georg W. Kreutzberg, head of the basic science branch of the Max-Planck-Institute of Psychiatry. A few months earlier, I had returned from Boston to join the Institute of Neuropathology of the University of Munich. I had known Henry deF. Webster for several years. His inquiry made us discuss in great detail the question of whether material from Alois Alzheimer's research could have been preserved. Yet after talking to a fair number of people, we did not come up with a definite answer, and I therefore wrote back to Henry deF. Webster on November 17, 1992:

As it appears, there are no slides of Alzheimer's research... available to us. Infact, it seems extremely unlikely that they still exist... From talking to Prof Mehraein, the good news is that this answer is not 100%, because there is an extremely remote chance that remainders of Alzheimer's materials could have traveled anonymously to our Institute... Yet, there is no catalogue whatsoever or any cross-reference to positively identify candidate slides, and we are therefore not only not able to provide Dr. Fujisawa with slides he could use but, unfortunately, also not with a definite answer to the question whether they do or do not exist... With public interest in Alzheimer's disease growing, I personally think that funds should be made available in the future to answer the above question satisfactorily. Special funding will be necessary, however, since a pertinent search seems likely to take not only months but years of detective work.

In view of the fact that my note to Henry deF. Webster sounded quite discouraging, the following letter from Kohshiro Fujisawa (Figure 1c), dated December 11, 1992. came quite unexpected:

As (a long time) has passed since Alzheimer worked on these two brains in Munich and there have been two devastating world wars since, I quite agree with you that there is left only a faintest hope to rediscover these brains somewhere in Munich. However, I believe in a

miracle. I believe because (1) you German people have a world renowned propensity for die Ordentlichkeit (orderliness) und die Pünktlichkeit (punctuality). These brains must have been kept with great care. I believe in (a) miracle because (2) these two brains of Alzheimer disease are... not typical of the disease... These two original cases of Alzheimer disease could be an irreplaceable source of inspiration. We should go back and look into those brains and rediscover what he thought he discovered therein, if it were possible... I hope to visit Munich next year to follow the path that once the renowned and outstanding neuro-pathologist/psychiatrist stepped on ninety years ago...

I was struck by the great enthusiasm of Kohshiro Fujisawa whom I did not know personally at the time and whose laboratory was located at the other end of the world. Consequently, I decided to embark on a systematic search and to get the original references mentioned in his letter as a first step. Clearly, without Kohshiro Fujisawa's letter, this project would not have been started.

The Institute of Neuropathology in Munich was founded in 1965 originating from the Institute of Pathology of the University of Munich. Thus, there is no direct connection to the Nissl-Alzheimer-Spielmeyer tradition which is rooted in the clinical neurosciences. Yet, Parviz Mehraein who became head of the Institute in 1983 had trained at the DFA for almost two decades together with Gerd Peters, the successor of Willibald Scholz and Walther Spielmeyer. In the late 1980s, both the Psychiatric Clinic of the University of Munich and the Max-Planck-Institute of Psychiatry "cleaned out" old materials, part of which Parviz Mehraein decided to adopt for conservation purposes. Without his interest, the sections would most likely have been lost.

As Kohshiro Fujisawa correctly pointed out in his letter (Figure 1c), the two papers Alzheimer wrote are very different. The first paper essentially represents an abstract summarizing the presentation Alzheimer gave at the 37th Meeting of the Southwest German Psychiatrists (2). It does not contain any biographical information on Alzheimer's first patient, Auguste D. By contrast, the second paper (3) which has the format of a textbook chapter not only gives a detailed review of the histopathological features of Alzheimer disease but also

Figure 1. (Opposing page) **a.** Henry deE. Webster (left) and Kohshiro Fujisawa (right) at the 1993 Annual Meeting of the German Society of Neuropathology in Berlin. **b.** Photograph of Kohshiro Fujisawa with his electron microscope at the Metropolitan Institute of Neuroscience in Tokyo shortly before his retirement from the Institute in 1996. **c.** Fujisawa's letter dated December 11, 1992. **d.** Table with stored archival material in the basement of the Institute of Neuropathology of the University of Munich (1993). Photographs courtesy of K. Fujisawa.

presents a very detailed clinical history of a second patient Alzheimer had seen at the hospital, Johann F. (4). It is important to note at this point that Alzheimer was always interested in clinico-pathological correlations and therefore, in contrast to his former teacher and colleague Franz Nissl who primarily worked as an experimenter, he concentrated his research efforts on human material. This explains why Alzheimer's second paper gives a very detailed clinical description of the patient along with several dates in addition to a very carefully written histopathology. As a result, the biographical data of the second patient described by Alzheimer were the logical starting point of our search.

Admission report provides missing link

After a few weeks, the autopsy book of Kraepelin's clinic was found in the basement (Figure 1d) of the Institute of Neuropathology of the University of Munich (4). One entry could be identified which shows the date of death of Johann F., his full last name, and a case number. Shortly thereafter, histological slides carrying the same last name as well as the case number, 784, were identified. A report issued upon admission of Johann F. to the hospital provided the missing link between these pieces of evidence by showing both the patient's first and last name as well as his date of birth. In order to confirm the actual age of the tissue sections, a comparative analysis of the ink used to label them was performed by specialists from the Bavarian State Bureau of Criminal Investigation. During the course of the study it also became clear that it was most likely the case of Johann F. which convinced Kraepelin to name the disease after his co-worker, Alois Alzheimer (5).

Auguste D.

In the meantime, public interest in the history of Alzheimer's disease was sparked by several publications (6-8). Maurer and co-workers discovered the clinical notes of Alzheimer's first case, Auguste D., in Frankfurt (8). In her brain (9), Alzheimer saw neurofibrillary tangles for the first time. In contrast, Alzheimer was not the first to report on amyloid plaques which had been previously described by other researchers including Fischer and Redlich (10). Analysis of the writings in the autopsy book of Kraepelin's clinic which had already served to identify the tissue sections belonging to Johann F. (4) showed referrals also from other hospitals outside Munich, including Frankfurt. One such entry, 181, contains a date which matches the time of Auguste D.'s death, as well as her last name allowing identification of the case (9, 11).

The material from Alois Alzheimer's two original patients totals more than 400 well preserved tissue sections. It is of very high quality from a technical point of view and a beautiful inspiration to neuromorphologists. We are currently preparing an atlas of all tissue sections which shows histological details of the different stains together with unpublished technical and historical information. This atlas will be made available on the World Wide Web.

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