

Simple observations, Great breakthroughs

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Simple, astute observations have led to some of the great breakthroughs in science and medicine. Be it the Newton's law of gravity or Archimedes principles, they made humble beginnings in simple observations. In the field of medicine, observation of an unwanted bread-mould growth on culture plate or milkmen's immunity to smallpox had paved way for penicillin and smallpox vaccine respectively. Not all observations are as dramatic though. From the field of psychiatry, let us retrace the story leading to recognition of a new disease entity, Alzheimer's disease.

Story of observations culminating in Case Report by Alois Alzheimer

Alois Alzheimer (1864-1915) joined 'The Municipal Asylum for the Insane and Epileptic', Frankfurt in the year 1888, nearly six months after he graduated from medical studies. With a wonderful team, including Nissl (of *Nissl's granules* fame), they transformed the asylum into a sound psychiatric clinic, where two concerns were foremost: First, avoiding use of physical restraint in patients; Second, the promotion of research to discover reasons of psychosis, through autopsies and neurological studies. Alzheimer had learnt the use of microscope and histological techniques at the laboratory of Kolliker in his university, which were put into good use in his career. Over next decade, he continued to work on a variety of neuropsychiatric topics, which earned him a reputation of '*The Psychiatrist with a microscope.*'^{1,2}

In the year 1901, a 51 years female patient, Auguste D, was admitted to the Frankfurt asylum. Over previous six months, she had begun to suffer from a delusion that her husband was seeing another woman. She had started making frequent mistakes in cooking, wander restlessly, had referential and paranoid ideas, forgetfulness and at times, appeared terrified that she is going to die. Alzheimer interviewed her the day after admission, and following are the excerpts³ from the notes he personally wrote:

What is your name? *Auguste* And you surname? *Auguste*

What is your husband's name? *Auguste, I think*

How long have you been here? *Three weeks*

What are you eating? *Spinach (while eating cauliflower and pork)*

Of the 32-page document of the patient, six pages were written by Alois Alzheimer in which he detailed his clinical observations, mental state and interviews of patient. The illness started at a relatively early age, much before her old age and appeared different from other types of *insanity*. Alzheimer was convinced that the case of Auguste is an extraordinary one, and certainly different from other patients in asylum. Interestingly, same man would go on to make another remarkable laboratory observation 5 years down the lane.

Alzheimer moved out of Frankfurt to join Kraepelin in 1902, who appointed him as the director of a Cerebral Anatomical Laboratory, which became one of the best laboratories in their times. Working closely, they sought to *discover neuropathology of psychosis*. In the year 1906, after five years of progressive psychiatric illness, Patient Auguste D died after complicated pneumonia and septicemia. The doctors at Frankfurt called Alzheimer to inform him of patient's death and sent him

the autopsy samples. Alzheimer used Bielchowsky's silver impregnation technique, a powerful microscope made by Zeiss and best available Camera lucida of the day and observed, *for the first time in history*, the microscopic lesions later known as Neurofibrillary tangles. Though these lesions appeared similar to lesions seen in old age, but were more marked and had occurred in a pre-senile patient. Six months later, Alois Alzheimer presented his findings at 37th assembly of South-west German psychiatrists, titled "*On a Peculiar, Severe Disease Process of the Cerebral Cortex.*" Well to his surprise, there were no comments from audience. Perhaps, his colleagues did not understand! He went ahead to describe it in more detail in published case report, ⁴ referring it as a 'new clinico-pathological entity.'

It was Kraepelin who recognized the significance of these findings (Working at same place, he had given concept of Dementia Praecox, while Alzheimer described Dementia!) and incorporated them into his 'Textbook of Clinical Psychiatry'⁵ in year 1910 with a brief mention as "*Alzheimer described a group of cases that showed severe neuronal alternations...*" Kraepelin referred to it as 'Alzheimer's disease'. These neuronal alterations were, however, believed to occur primarily in pre-senile cases, however later on they were found to be present in senile cases as well. Nonetheless, till then, only one form of insanity, General Paresis or *dementia paralytica*, had been discovered (which could be subject of another interesting story) to have a clear pathological basis and Alzheimer's disease became second.

Ironically, not a single tribute on his death in 1915 mentioned this significant discovery. His findings were lost in theories of elderly neglect and psychoanalytic explanations of dementia for next 50 years. In 1960s, many scientists sought to understand the old age and dementia, of which Martin Roth et al⁶ published a historical article in *Nature*, re-confirming the relation between density of plaques and old-age dementia. From then on, there was no looking back and conducive social, political and philanthropic support made Alzheimer's disease one of most researched and well-funded of diseases.

Interestingly, what is now heralded as disease of the century was observed so meticulously and brilliantly by a scientist whose work and vision were ahead of time.

Footnote: In year 1995, Maurer and colleagues retrieved the original records of patient, Auguste D from Frankfurt university clinic, after several unsuccessful search attempts for two years. Original pathology slides were found at University of Munich in 1997. Almost a century later, scientists finally laid to rest the doubts of a few researchers that it could have been a vascular dementia and re-confirmed all the original findings of Alzheimer.

References

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