

# KONSTANTIN N. TRETIAKOFF IN BRAZIL

## A historical perspective and discussion of his contribution to Brazilian neuroscience

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**Abstract** – The Hospício de Juquery, near the city of São Paulo (Brazil) was founded in 1896 and after few years it was decided that the institution should have the best possible facilities to study neuropathology. In 1921, a young psychiatrist, Antonio Carlos Pacheco e Silva was sent to the Hôpital de la Salpêtrière (Paris) to study neuropathology. There, Pacheco e Silva (later Prof. Pacheco e Silva) befriended Konstantin N. Tretiakoff accepted an invitation to become the first Chairman of the newly created neuropathology department of the Hospício de Juquery. During his stay in this institution, from 1922 to 1924 or early 1925, he worked very hard and produced many publications. Here we present and comment some of the papers he published in a Journal (Memórias do Hospício de Juquery – “Memoirs de l’Hospice de Juquery”), which had been recently created and present some information of this poorly known period of his life.

KEY WORDS: Parkinson’s disease, Tretiakoff, substantia nigra, Brazil.

### Konstantin N. Tretiakoff no Brasil: uma perspectiva histórica e discussão de sua contribuição à neurociência brasileira

**Resumo** – O Hospício de Juquery, perto da cidade de São Paulo (Brasil) foi fundado em 1896 e depois de poucos anos o Prof. Franco da Rocha, seu fundador, e os demais responsáveis pela instituição, com a ajuda do Governo do Estado de São Paulo, decidiram que deveriam criar as melhores instalações para o estudo da neuropatologia. Em 1921, o jovem psiquiatra Antonio Carlos Pacheco e Silva foi enviado para o Hôpital de la Salpêtrière (Paris) para estudar neuropatologia. Nessa instituição, Prof. Pacheco e Silva tornou-se amigo de um jovem neuropatologista, neurologista e psiquiatra russo Konstantin N. Tretiakoff que aceitou o desafio de chefiar o recém criado Departamento de Neuropatologia do Hospício de Juquery. Durante sua estada entre nós, de 1922 a 1924 ou início de 1925, ele trabalhou muito aplicadamente e produziu muitas publicações. Aqui nós apresentamos e comentamos alguns destes trabalhos que ele e seus associados publicaram em um novo Jornal (Memórias do Hospício de Juquery – “Memoirs de l’Hospice de Juquery”) que circulou entre 1924 e 1927. Ademais, apresentamos algumas informações sobre esta parte menos conhecida de sua biografia.

PALAVRAS-CHAVE: doença de Parkinson, Tretiakoff, substância negra, Brasil.

In 1896 the Hospício de Juquery (Hospice de Juquery, Juquery Hospital for Mental Diseases) was founded by Prof. Franco da Rocha, after many years of planning and building the wide wards and administrative buildings in a large farm 60 Km distant from the city of São Paulo (capital of the state of São Paulo in the south-eastern part of Brazil). This mental institution many years later became one of the largest hospitals for mental diseases existing in the

world. From the thirties up to the eighties in the last century, the numbers were astonishing, including 20,000 to more than 30,000 in-patients admitted in the wards and many living in remote areas of the farm in primitive houses, providing their own food and resources. Some were even unknown to exist by the administration and never seen by any doctor, receiving no treatment whatsoever. In those days, many mentally ill persons were brought to the

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institution by family members and as time passed they stopped coming to visit and eventually moved to other parts of the country, leaving no address. Others were homeless people found in the streets of São Paulo, alcohol addicts and all sort of mentally deranged persons, with no family or address. So, a considerable proportion of patients were left under the institution care and there was no place where they could be sent to, in case of a discharge. Since the initial years Prof. Franco da Rocha had been applying to the local government for the creation of a Pathological Anatomy Laboratory as found in the best mental institutions of Europe and USA. The amount of diverse cerebral and clinical diseases that could be found and studied was so immense and probably with regional importance, that made a Pathology Laboratory of utmost importance. In 1921, a young psychiatrist Antonio Carlos Pacheco e Silva was sent to Salpêtrière, in Paris, to study neuropathology and, on his way back to Brazil, to create the new Neuropathology Laboratory in the Hospício de Juquery. During his stay at Salpêtrière Pacheco e Silva (who later became the laureate Prof. Pacheco e Silva) met Konstantin N. Tretiakoff as chief of the Salpêtrière Laboratory and became friend of this Russian scientist who had produced an important study demonstrating the Lewy bodies in the substantia nigra of patients suffering from Parkinson's disease. Konstantin Tretiakoff's doctoral dissertation "Contribution a l'étude de l'anatomie pathologique du locus niger de Soemmering avec quelques déductions relatives à la pathogénie des troubles du tonus musculaire et de la maladie de Parkinson" was presented in 1919. At the end of 1922, finally the Neuropathology Laboratory was inaugurated and Konstantin Tretiakoff accepted to be nominated the Head of the newly created lab<sup>1</sup>. What a challenge might have been to this Russian coming to a distant country to live in a farm away from the relatively small city of São Paulo (nowadays with 15 million people!), leaving Salpêtrière and Paris, with his mind focused at the immense work still to be done. In the previous two years 250 necropsies had been made by the local staff and the brains and spinal cords were preserved in formalin for study. The laboratory was rapidly equipped with the best facilities as possible, recent and modern microscopes, all sorts of equipments needed for surgical and necropsy studies, the best and more recent histological staining techniques used in neuropathology and complete photographic facilities. An extensive library on psychiatry, neurology, general medicine and, especially, neuropathology, already existing was enlarged by new acquisitions. Although buildings, labs, library and other facilities were the state-of-the-art, the treatment offered to the patients were as archaic as in any other mental institutions of the world. The quality of medical treatment corresponded to the pre-neuroleptic era. Rooms to isolate

agitated patients, locked like in a prison, physical restraint, the use of cold baths, insulin-therapy for hypoglycemic coma, malariotherapy and pyreotherapy (injecting daily sulphur compounds to increase body temperature up to 42–43°C) and electro-convulsive therapy (ECT applied by the Charlette equipment) were all regularly used.

The new era of psychiatric pharmacological treatment started with the introduction of chlorpromazine in the early 50's, turning the treatment story into the current practice, with the new antiepileptics, antidepressants, mood stabilizers, tranquilizers, hypnotics, modern atypical neuroleptics, new psychotherapeutic interventions and leaving ECT (applied under anesthesia with modern equipment) for a small proportion of refractory patients.

Tretiakoff took no longer time to establish a febrile period of work in the laboratory and in the wards or in the out-patients facilities, as well. His holistic interests exceeded the pathological material including personally examining patients and discussing general medicine, neurology, psychiatry and, of course, neuropathology, as it was usual for the tradition of the best specialists in Europe, in those days. Figure depicts one rare occasion of leisure with Tretiakoff along with AC Pacheco e Silva and his brother traveling on their way to a beach resort (Santos) near São Paulo. In 1924, Tretiakoff and many other Brazilian colleagues published the first Volume of a newly created Journal, the *Memórias do Hospício de Juquery* ("Memories of the Juquery Hospital for Mental Diseases; Memoires de l'Hôspice de Juquery"). This yearly Journal was published in a bilingual edition (Portuguese and French), and we could find four Volumes, from 1924 to 1927, in the Public Health School Library, in São Paulo. Unfortunately, two years ago, a tragic fire destroyed completely one large building of the institution, where all patient files, the complete library and the historical documents were being preserved, consuming the entire material. Most of the historical aspects concerning Tretiakoff's stay in Brazil which are now being presented here were given to one of us (Lafa) by personal interviews to the few descendants of those who worked in the Juquery over the years<sup>2</sup>. In the first Volume (1924) Tretiakoff's contribution was paramount, being the sole author or one of the authors in almost every paper. We will briefly comment on some of these papers. In the last two decades, according to the new regulations for Mental Health from the Brazilian medical authorities, all mental institutions were practically closed, favoring out-patient facilities or day-hospitals for short in-patient treatments. Nonetheless, many chronic patients abandoned by families and having no where to live are still being under care in institutions.

*Les "plaques cyto-graisseuses" dans les maladies mentales diverses et l'origine de ces plaques*<sup>3</sup>, authored by C Tretiakoff. In 1922, Laignel-Lavastine, Tretiakoff and

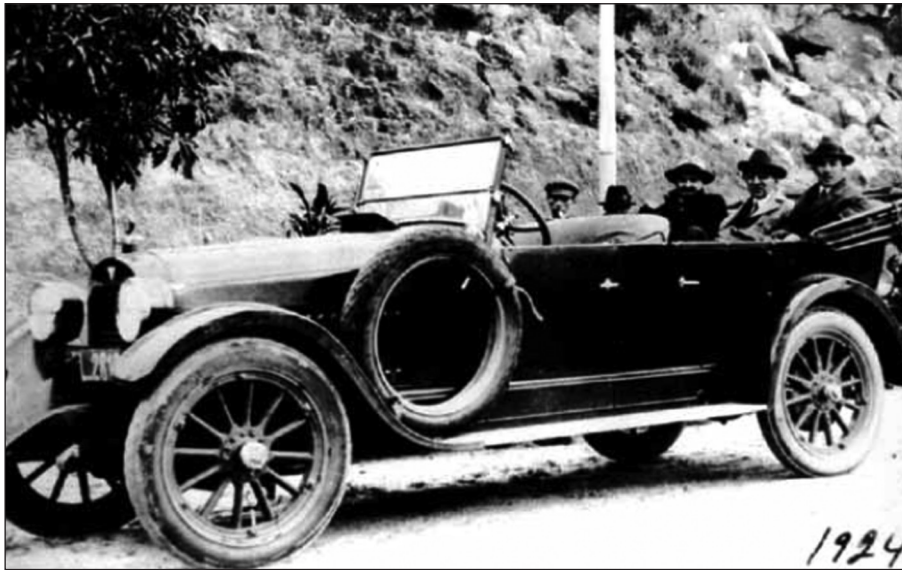


Figure. Tretiakoff (left, bearded), AC Pacheco e Silva (center) and his brother, D Pacheco e Silva (right, an engineer), boarding a convertible Hudson 1921 on their way to Santos, a beach 60 Km. away from São Paulo, for a holiday trip (1924).

Jorgoulesco published their studies in the “plaques cyto-graisseuses” as they called these lesions found in the striatum in three cases of “*démence précoce hébéfreno-catatonique*”<sup>4</sup>. Face to the vast anatomo-clinic material at his disposal at the Juquery he decided to expand his research on this topic. These plaques were localized amounts of fat material found in the striatum and cerebral cortex, completely absent in the white matter, more intensely found in the anterior parts of the striatum, in the Ammon’s horn and temporal circumvolutions. At Juquery he studied the brains of 51 patients who had suffered from diverse mental or neurological diseases, according to the nosology of that time, as follows: *démence précoce hébéfreno-catatonique* – 15 cases, *démence précoce paranoïde* – 5 cases, *délire hallucinatoire chronique* – 3 cases, *cysticercose cérébrale* – 4 cases, *alcoolisme* – 2 cases, *démence senile* – 2 cases, *artério-sclérose avec ramolissement* – 1 case, *psychose maniaco-dépressive* – 5 cases, *depression mélancolique (enterite chronique, cachexie)* – 5 cases, *paralysie générale* – 5 cases, *encephalopathy infantile* – 1 case, *meningite tuberculeuse* – 1 case, *épilepsie essentielle* – 1 case, *hystérie* – 1 case. He could find the fat plaques in the first six categories of diseases. The presence of the plaques was unrelated to the final diagnosis of death of the patients. In the article Tretiakoff made a comprehensive review of the current knowledge of the role of lipids in human metabolism, which was quite remarkable. As a final remark he states that, in spite of a systematic search of these plaques, no firm opinion as to the nature or meaning of these structures could be made, but rather “*l’idée que ces formations ne seraient autre chose que*

*l’expression histologique d’une réaction lipidienne humorale au niveau des centres nerveux*”. One can speculate on the existence of these plaques as true neuropathological events or the consequence of some technical difficulty with the conservation or dealing with the material.

*Contribution à l’étude de la cysticercose cérébrale et en particulier des lésions cérébrales toxiques à distance dans cette affection*, authored by C Tretiakoff and AC Pacheco e Silva<sup>5</sup>. The very first case of human extra-cerebral cysticercosis published in Brasil was of 1881, in Bahia, by Prof. Pedro Severiano de Magalhães. A cerebral cysticercosis case was first published by Prof. Miguel Pereira in the National Mental Hospital (Hôspice National des Aliénés) from Rio de Janeiro, in 1905<sup>5</sup>. At the Juquery, Geraldo de Paula Souza in 1912 was the first to find parasitic cysts in the brain of an epileptic patient. In the first 250 necropsies made at Juquery, they could find 9 cases of brain or spinal cord cysticercosis, making a detailed pathological study. The patients were alcohol abusers, psychotics, epileptics, syphilitics or demented, in some coexisting these pathologies in different combinations. The structure of the cysts, some still viable, or degenerating with inflammatory reactions in the surrounding areas and others already calcified (natural healing) were described in detail. Remote effects such as inflammatory reactions in the ventricle walls, the meninges or blood vessels were seen and described, commented and discussed its role in the symptoms presented. It seemed clear that the parasite produced a toxic effect which would develop the inflammation elsewhere. The inflammation pattern always included eosinophils and plasma cells, along with the neutro-

phils and monocytes. A particular case of inflammation of the meninges in the spinal canal with paraparesis was discussed in depth. The conclusion was that cysticercosis had to be considered as an important social burden due to the prevalence (4% in their material) and to the irremediable nature of the disease at that stage.

À propos de quelques lésions vasculaires dans la psychose maniaco-dépressive, by C Tretiakoff and F Marcondes Vieira<sup>6</sup>. The episodic psychoses, as well as other cyclic mental disturbances were poorly understood in its nature and pathogenesis. There had been a growing concern that vegetative or vasomotor disturbances could be involved in the pathogenesis. So far, the etiology of the “*cyclothymies*” had been related to traumatism, emotional shocks, infections or intoxications. The possibility of some unknown plasmatic factor, like hormones, substances formed due to lesions in the kidneys, liver, derangements of the metabolism (hyperglucemia, uremia, etc.) or troubles with internal secretions, be the trigger factor of the episodic mental abnormalities had been put forward by many authors. *En resumé, il parait difficile de mettre les manifestations cyclothymiques sur le compte d'une seule cause, toujours la même; mais, sans qu'on puisse préciser, à l'heure actuelle, l'étiologie de cette affection, il semble que des intoxications, variables suivant les cas, jouent un rôle important dans le déterminisme des accès cyclothymiques.* How close they were to properly understand the nature of abnormal mental processes; if they had means to find the role of neurotransmitters and/or neuromodulators in its minute quantities in the brain (“intoxications” from the CNS itself!) or the ability to show the activation of regional blood flow as a consequence of the increase in metabolism of a given area of the brain, as we do today! If we make small substitutions of words the text would turn into the current knowledge (...*les manifestations cyclothymiques sur le compte d'une seule cause, toujours la même; mais sans qu'on puisse préciser, à l'heure actuelle, l'étiologie de cette affection, il semble que des intoxications* (excessive neurotransmitters/neurotransmission, receptor up or downregulation)... *dans le déterminisme* (genes, DNA, molecular genetics) *des accès cyclothymiques.*

In this paper Tretiakoff and Marcondes Vieira studied a case of *melancholia*. This patient had lasting bouts of depression but occasionally, hypomaniac spells of variable duration, needing to be admitted to the Juquery on several occasions. It was clearly a case of bipolar affective disorder (*psychose maniaco-dépressive*), having a certain degree of mental decline (at 41 years of age!). The patient died years after a prolonged time at the Juquery, from a cerebral hemorrhage, probably due to an acute and devastating hypertensive crisis. The terminal apoplexy crisis had been seen by many authors as an endpoint of manic-depressive psychosis and there had been some specu-

lations on the role of pre-existing vascular pathology of this type in the mental pathology. The authors, although not endorsing these views entirely, made no special effort to deny its role.

*Contribution à l'étude des troubles moteurs et “psychomoteurs” dans certaines formes d'hypertonie musculaire, particulièrement chez les parkinsoniens.* By C Tretiakoff and AC Pacheco e Silva<sup>7</sup>. For a long time much attention had been given to many polymorphic and extraordinary clinical manifestations presented by “parkinsonian” patients, seen as a consequence of lethargic encephalitis or from the Parkinson's disease itself, as well as in many other instances of mesencephalostriate impairment where movement disturbances appeared. The “*kinésie paradoxale*”, the “*progression metadromique*”, the “*mutisme parkinsonien*”, the “*gestes intentionnels stéréotypés*”, etc, were all fine examples of motor or “psychomotor” phenomena of difficult interpretation, frequently being misdiagnosed as “*pithiatisme*” (of hysteric origin). The authors studied two cases, one of a complex cervicofascio-brachial spasm and the other of a post-encephalitic parkinsonism and made a thorough discussion on the clinical manifestations, comparing the phenomena, giving pathophysiological suggestions, trying to shed some light in this still obscure area of movement abnormalities and provoking new insights in the readers minds.

The first case was a young 16-years-old a white Brazilian who had the epidemic lethargic encephalitis in 1920. The disease started on June, 29<sup>th</sup> with pain in the arms, insomnia, psychomotor agitation. After two days he became severely somnolent, presenting diplopia and oniric delusions. This persisted for 7 days. On July, 15<sup>th</sup> a neurological examination disclosed a parkinsonian state. Beginning on October an abnormal psychic state with restlessness, insomnia and irritability appeared. Intense salivation, lateropulsion and an *hémiplégie parkinsonienne* on the right side was clear. The authors describe a very detailed neurological examination. The bulk of the description is a florid parkinsonian state as we would describe it today. However, many terms and descriptions are worth presenting because they may illustrate how difficult were for them to understand and properly name the abnormalities. As pointed before they called parkinsonian hemiplegia on the right side a movement abnormality clearly related to bradykinesia and rigidity on that side. The search of *adiadococinésie* (a cerebellar examination) with alternate supination and pronation of the hands, produced a gradual slowness of the hands until they arrested the movement, in a shorter time in the right side. This motor block due to the bradykinesia was understood as a *pseudo-adiadococinésie*. Another interesting phenomenon they had observed was the *progression metadromique*: while his walking was very slow, he could run easily as well as jump dis-



tances of a meter or so. A fluctuation in his ability to walk was striking and the patient had a faster walk in the night as compared to the day and in the morning it was easier and faster than in the evening. These phenomena were called as examples of *kinésie paradoxale*.

The second case was a 36-years-old Italian born white man. The present disease started when he was 12-years-old with involuntary internal rotation of the right arm. During the next ten years this symptom persisted as an isolated phenomenon, producing little discomfort to him. At school he proved to be a diligent pupil, having a nice handwriting with his right hand and a good ability to the drawing. He was considered to have good skills in gymnastics, playing normally with his mates. After his 18<sup>th</sup> birthday he started working at a jeweler shop and eventually became an efficient jeweler. Slowly but progressively the involuntary spasms in the right arm increased in intensity, impairing his handwriting and his work, so that at the age of 20 he had been forced to shift to his left hand in order to keep his work. Five years later the muscle spasms started to happen in his face and his speech changed. He was examined at the institution on April, 1924. He presented multiple muscular spasms including the face, neck and both upper limbs, specially the right one. The muscles of the neck were very enlarged, like of a boxer and the left sterno-cleido-mastoid muscle was contracted and stiff. The peri-oral muscles were constantly contracting and the frontal wrinkles were accentuated, more on the right side. The right shoulder was elevated. The right upper limb was internally rotated and exhibiting slow rotational movements. The spine had a *scoliose à triple coubure, dorsale droite, lombaire gauche*.

Literally understanding the meaning of the words, the two patients had different phenomena being observed but defined as having the same origin. This could be taken as one important difficulty the investigators of that time had to really understand the meaning of words used to define neurological abnormalities, specially when movement disorders were being described. They had access to the written literature but seldom they could be present to the neurological examination made by their masters. So, without any imaging technique available they had to imagine how the description fitted in their own patients. The neurological language became more universal and the meaning of any definition of movement or posture abnormality became clear to all who deal with this part of neurology after we started recording the patients with portable cameras. One image worth more than one thousand words, it's said. In a summary, they did not recognize the case of a muscular dystonia (torsion dystonia) although mentioning Oppenheim's *dysbasia lordotica*.

For the sake of editorial space the next Tretiakoff's contributions will be very briefly presented. *Un cas de*

*sclérose latérale amyotrophique pseudo-polynevritique, observée chez une aliénée, atteinte de tuberculose intestinale*, by C Tretiakoff and M de F Amorim<sup>8</sup>. This paper deals with an interesting case of a woman with a chronic diarrhea developing an altered mental state and motor signs of central and peripheral origin. The pathology suggested an amyotrophic lateral sclerosis but she had probably a polyneuropathy associated to it.

*Étude des granulations pigmentaires peri-cellulaires d'origine hématique dans un cas d'alcoolisme avec troubles mentaux*. By C Tretiakoff and F Cintra do Prado<sup>9</sup>. They describe a very interesting case of a 46 years-old white male, of Italian origin, who had been a constant drinker for many years. The admittance diagnosis was *confusion hallucinatoire aigue alcoolique, à pot-suspense* (acute alcoholic abstinence). He persisted in the hospital, showing a stabled mental disability. Fifteen months later he died of pulmonary tuberculosis.

The anatomo-pathology of the central nervous system was quite unremarkable but their attention was attracted to *une infiltration pigmentaire très prononcée de la couche des cellules de Purkinje*. This pigmentary infiltration affects both the meninges and the vascular adventitia in the cerebellum, as well. Tretiakoff and his colleague could not find any definite idea about the meaning of these pigments and concluded that they derived from circulatory congestion and hemorrhages (*poussées congestives et les hémorragies*).

*Une forme particulière du syndrome pédonculaire alterne*. By C Tretiakoff and AC Pacheco e Silva<sup>10</sup>. This case description offers a good discussion on the anatomical correlation of an alternate peduncular syndrome which shows some differences to the known Weber syndrome. The authors propose a new alternate peduncular syndrome named *le syndrome nigro-pyramidal*.

Three small final papers close C Tretiakoff contribution to this volume, as follows: "*Cavités anfractueuses dans un cas de syndrome cérébelleux, survenu chez une démente précoce*". By C Tretiakoff and AC Pacheco e Silva<sup>11</sup>, "*Troubles mentaux dans deux cas de myopathie primitive*". By C Tretiakoff and AC Pacheco e Silva<sup>12</sup> and "*Démence précoce catatonique, datant de 21 ans, chez un shyphilitique*". By C Tretiakoff and M de F Amorim<sup>13</sup>.

The final part of this superb work is a comprehensive review of the papers presented by numerous masters of that time, specially of the French literature, like Souques, Babinski, Froment, Pierre Marie, Levy (writer's cramp), Claude, K Wilson, Foix et Thevenard, and many others. After 84 years this discussion still holds as an useful tool to understand the importance of neurological semiotics to the knowledge of pathophysiology before the modern technology was introduced in neuroscience. This is a breathholding discussion worth to be read.

**FINAL REMARKS**

As far as the reasons why Tretiakoff came to Brazil, probably in the year of 1922, very little is possible to add. There is no written document that we could find giving his insight on this point. Tretiakoff had been admitted as an externe in the L'Assistance Publique des Hopitaux de Paris, after having failed the highly competitive examination to become an interne (a better status for an upper education in neurology). Eventually he decided to develop a career in neuropathology and was appointed Chef du Laboratoire de la Clinique de Maladies du Systeme Nerveux, under Prof Pierre Marie<sup>14</sup>. It is probable that his career prospects in Paris would not be very promising. This fact may have had an importance in his decision to accept the challenge of coming to São Paulo. In addition, the flowering Brazilian culture and economy in the beginning of the twentieth century has made the country and particularly Rio de Janeiro, a popular and attractive place for visitors and emigrants. Looking through the great amount of research and work done in the small time he has spent in the country, one can speculate that he was very pleased with his time here. We could not find any firm statement with the reasons for his return to Europe, probably at the end of 1924 or soon after. Reviewing the volumes 2, 3 and 4 (1925, 1926 and 1927) of Memórias do Hospício de Juquery we were not able to find any other Tretiakoff's contribution, what make us think that he probably had already left Brazil by then. One speculation that may be added is one fact that may have had some importance in his decision to get away as fast as possible from Brazil. In July, 1924, a Revolution took place in Brazil by the opponents to the ruling president Arthur Bernardes, and many skirmishes occurred in São Paulo. During the 23 days that this so-called Revolution lasted over 500 people died in São Paulo. Imagine what might've come to the mind of a Russian man, who had witnessed the Great War, and how these facts may have influenced his decision to leave the country. Apart from these speculations, he had been anxiously waiting for a sign from his fellow scientists from Russia concerning the possibility of recovering his Russian citizenship. This came in form of a letter from his old friend and mentor Vladimir Bechterev, posted in march, 31<sup>st</sup>, 1924, telling him that an effort had been made in his behalf so that he could restore his citizenship. This letter was reproduced in full in our recently published paper<sup>14</sup>, as well as the details of the rest of his career as Chairman of the Neuropathology Department at the Saratov Medical Institute. For the Brazilian neuropathology, clinical neurology and psychiatry his stay was a great privilege and we would like to honor the memory of this outstanding master of neuroscience.

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