Tuberous sclerosis or Bourneville disease: the birth of an eponym

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ABSTRACT

Bourneville brought about groundbreaking reforms in the teaching and practice of medicine and spearheaded many initiatives in the fields of hygiene and public health. His most important contribution was transforming the boys' ward at Bicêtre, in a dismal state on his appointment in 1879, into a model medical-pedagogical unit aimed at rehabilitating and educating every child housed there –even the 'idiots', who until that time had been considered incurable and who were given little if any care or training.

Bourneville did not go down in history, however, for his efforts as a moderniser, but rather for his descriptions of tuberous sclerosis lesions in the brain of one such 'idiot' patient. Although his observation and published description of this princeps case could be said to be a fluke, Bourneville and his students studied and published an additional ten cases of tuberous sclerosis in the following years. This is an indicator of his overarching interest in idiocy, from its neuropathological basis to the care and education of affected patients.

This study presents the clinical and anatomical pathology features of cases published by Bourneville himself. The doctor was able to identify neuropathological lesions and renal tumours, but despite the detailed clinical examinations and autopsies of as many as ten cases, he did not detect or at least did not mention any of the other cutaneous or visceral signs of the disease now bearing his name.

KEYWORDS
Bourneville, tuberous sclerosis, idiocy

Introduction

An earlier article[1] presented a brief biography of Bourneville, with remarks on his tremendous political efforts in the areas of healthcare reform and practitioner training on the one hand, and his superhuman struggle to create a medical-pedagogical ward for institutionalised boys in Hospice Bicêtre. The result was an establishment that was unrivalled at the time.

When we examine the life and labours of Bourneville, it seems almost ironic that the doctor is remembered only for his description of a clinical case discovered by chance. However, he did go on to chronicle another ten cases, which reflects his assiduity as a researcher. Thanks to this disease, Bourneville's name remains alive, but it has been omitted from the lists of the great reformers contributing the most to the advance of medicine. This is patently unfair, particularly when we consider his achievements in comprehensive care for mentally disabled children.

At the beginning of the 19th century, after several twists of fate, Hospice de Bicêtre became a men's rest home (Hospice de la Vieillesse-Hommes) with the Salpêtrière serving the same role for women (Hospice de la Vieillesse-Femmes). Yet despite these names, some of the population housed by these centres was very far from elderly. Bicêtre had a large population of boys attended by an independent service. The boys were classified by dominant disease; those with the greatest mental handicaps were identified as 'idiots'. These children were considered hopeless cases and did not receive any type of care or education; rather, they were left cruelly to their fate in com-

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mon rooms. Upon his arrival, Bourneville described the situation as "sordid and shameful for l'Assistance Publique". He went on to dedicate many years of his life to improving and humanising care for children housed by the Bicêtre.[1]

Material and methods

This study is based on a review of Bourneville's original texts on tuberous sclerosis. All of these manuscripts are available on the Jubilothèque webpage (http://jubilotheque.upmc.fr/subset.html?name=collections&id=charcot). I reviewed each of the cases in order to provide a synopsis of all of Bourneville's observations within the context of his clinical and neuropathology studies of idiocy.

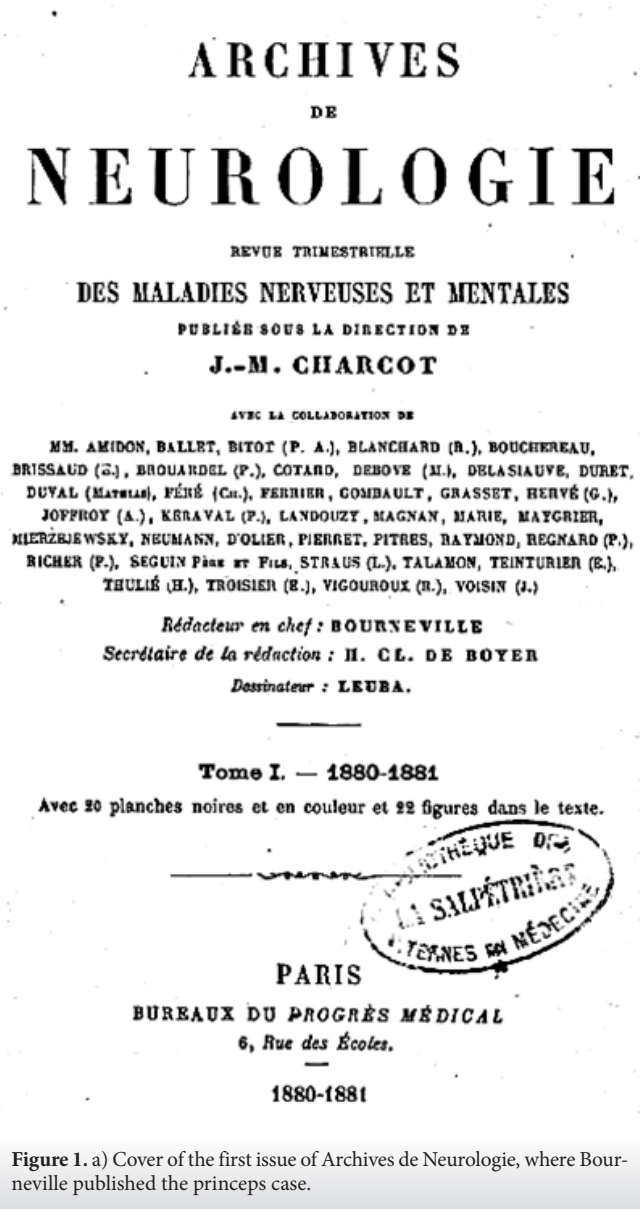
Results

The first case of tuberous sclerosis

Bourneville became head of the boys' ward at the Bicêtre in 1879. It could be said that through a mixture of pragmatism —his nature left him no choice but to throw himself into his assigned task—, the scientific curiosity inherited from Charcot, and the idealism that marked his personality and his political leanings, he decided to devote all of his energy to caring for mentally handicapped children in a long-term scientific, care-based, and educational project.

Bourneville observed the princeps case of tuberous sclerosis not at the Bicêtre, but rather in La Salpêtrière, where he was substituting for his teacher Louis Delasiauve.[2] This princeps case was included and remarked on in a well-known compilation of classic neurology cases.[3]

The first patient was part of a three-case series on anatomical pathology in idiocy (Figures 1a and 1b). Bourneville stated his intention to continue publishing more of the cases he had collected so as to present the neuropathological basis of idiocy and the means of treating it through education. Bourneville shows his true colours as a visionary reformer with this statement: it is clear that this was no mere anecdote or fleeting interest in a random patient, but rather a pre-conceived project. He added that "the patients would have had to be studied over many years" in order to have complete case histories. This was none other than Charcot's method, used in La Salpêtrière.



ARCHIVES

DE

NEUROLOGIE

REVUE TRIMESTRIELLE

DES MALADIES NERVEUSES ET MENTALES

PUBLIÉE SOUS LA DIRECTION DE

J.-M. CHARCOT

AVEC LA COLLABORATION DE

MM. AMIDON, BALLET, BITOT (P. A.), BLANCHARD (R.), BOUCHEREAU, BRISSAUD (E.), BROUARDEL (P.), COTARD, DEBOVE (M.), DELASIAUVE, DURET, DUVAL (Mathias), FÉRÉ (Ch.), FERRIER, GOMBAULT, GRASSET, HERVÉ (G.), JOFFROY (A.), KERAVAL (P.), LANDOUZY, MAGNAN, MARIE, MATGRIER, MIERZEJEWSKY, NEUMANN, D'OLIER, PIERRET, PITRES, RAYMOND, REGNARD (P.), RICHER (P.), SEGUIN Père et Fils, STRAUS (L.), TALAMON, TEINTURIER (E.), THULIÉ (H.), TROISIER (E.), VIGOUROUX (R.), VOISIN (J.)

Rédacteur en chef : BOURNEVILLE

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Tome I. — 1880-1881

Avec 20 planches noires et en couleur et 22 figures dans le texte.

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6, *Rue des Écoles.*

1880-1881

Figure 1. a) Cover of the first issue of Archives de Neurologie, where Bourneville published the princeps case.

The princeps case was L. Marie Pit—, institutionalised in 1867 at the age of three; she died in 1879 at 15 years of age. It is noteworthy that Bourneville's article indicates that the patient's medical history was based on information provided by her mother in March of 1879. It seems that after 12 years of hospitalisation, for the first time a doctor was taking notice of this patient. This is probably a good reflection of two tendencies. First of all, alienists had very little interest in the 'idiot children', who were their patients. Second, it shows that Bourneville followed Charcot's tradition of establishing

OBSERVATION III

SCLÉROSE TUBÉREUSE DES CIRCONVOLUTIONS CÉRÉBRALES : IDIOTIE ET ÉPILEPSIE HÉMIPLÉGIQUE.

Sommaire. — Absence d'antécédents héréditaires. — Emotions morales et attaques de nerfs pendant la grossesse. — Convulsions dans la première année. — Accès d'épilepsie à partir de 2 ans.

État de la malade en 1879. — Arrêt de développement physique — Idiotie. — Hémiplégie du côté droit. — Parésie du côté gauche. — Description des accès isolés (Epilepsie partielle). — État de mal ; Nitrite d'amyle. — Amélioration passagère. — Pneumonie ; mort.

Autopsie. — Ilôts de sclérose hypertrophique. — Leur distribution sur les deux hémisphères cérébraux. — Anomalie des olives, etc.

Pit.. L. Marie, âgée de 3 ans à son entrée à la Salpêtrière le 18 juillet 1867 (service de M. Delasiauve) [1].

[1] Nous avons recueilli cette observation alors que nous remplacions M. Delasiauve.

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Figure 1. b) Title of Observation III, corresponding to the first case with sclerotic lesions of the gyri.

a clinical-pathological correlation by taking down a detailed medical history so as to be able to subsequently link it to autopsy findings.

The parents of L. Marie were healthy and nonconsanguineous. The patient was the oldest of five children. The two that succeeded her died in infancy without convulsions; the other two, aged ten and seven, were healthy. There were no pathological signs during the mother's pregnancy or childbirth, and the girl had been fed by a wet-nurse for 14 months. During this time, she was seen to experience convulsions limited to the eyes. Seizures began when she was about two years old; they were described as "affecting her head most of all" with mild rigidity of the arms which would rotate slightly. Profound mental retardation meant she could not speak or walk, and she made stereotypic movements

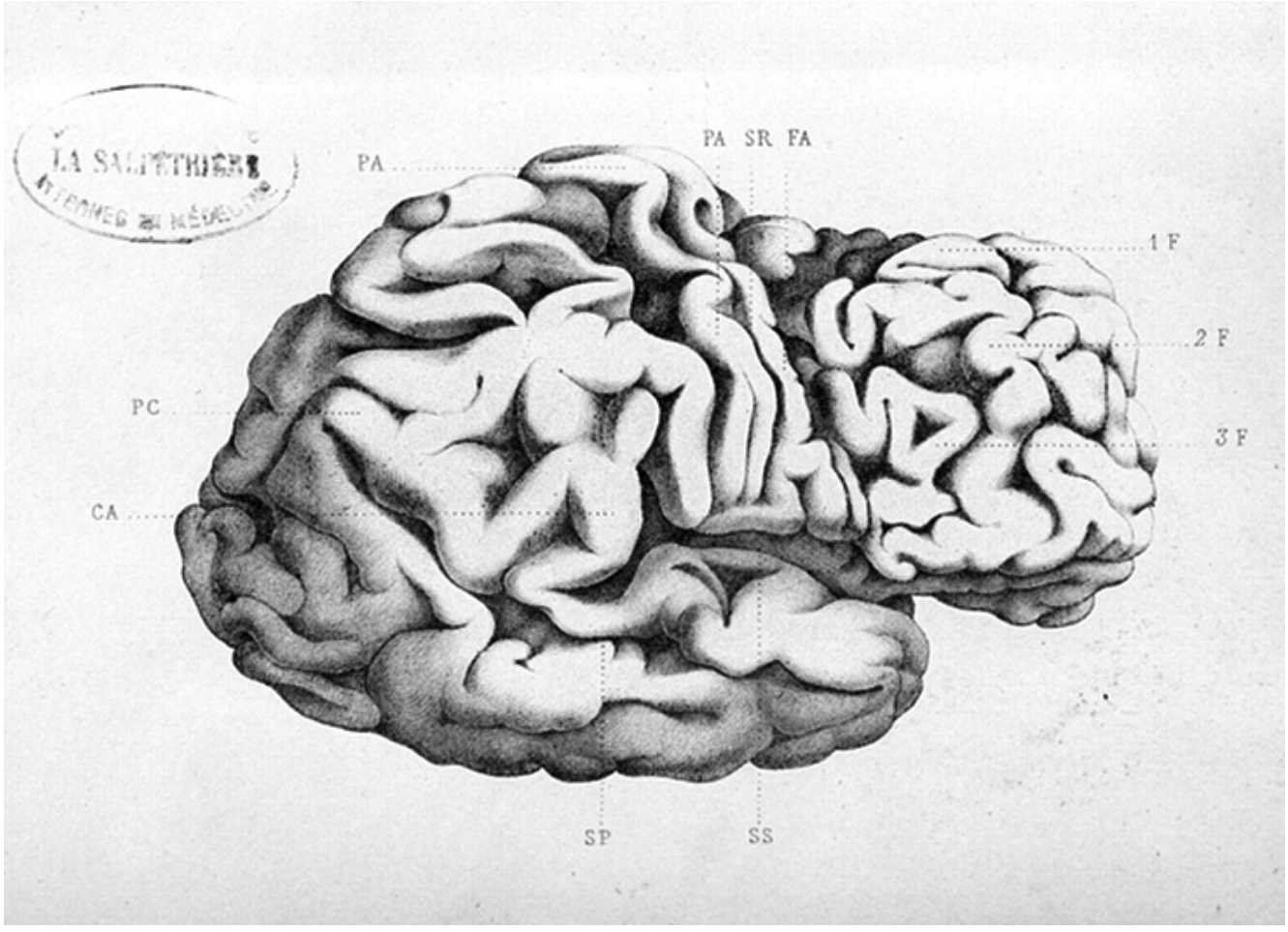

Figure 2. a) Drawing of the external aspect of the brain of the first patient, which shows sclerotic foci.

such as putting her hands in her mouth, or hitting them together.

An examination of her face revealed acne rosacea and pustules, in addition to a papular, vesicular eruption on the nose, cheeks, and forehead ("*acné rosacée et pustuleuse; de plus, eruption vesiculo-papuleuse confluente du nez, des joues, du front*"). She also had a few molluscum lesions on her neck. Her general health and physical development were very poor.

The neurological examination revealed paralysis of the right arm with joint rigidity. Her left arm was relatively mobile. Her right leg muscles were hypotrophic compared to the left with limited hip adduction and flexion and her right foot was flat, purplish, and clubbed. She bore scars from bedsores around the sacrum and trochanters.

Bourneville also described a seizure that he personally witnessed: "her eyes roll upward and to the left; the arms go rigid, the right more than the left, and draw together over her chest. Next, clonic convulsions could be seen in the right limbs, together with rapid twitching of the eyelids, followed by stertorous breathing and an issue of bloody foam". Seizures usually presented consecutively: "six last night, and two in the morning".

This account was followed by nearly daily notes on her progress, taken from that March until the patient's death on 6 May. Seizures were extremely frequent, with as many as 150 in one night. Most were similar to the one described above, but a few began as focal seizures in the right foot before becoming generalised. The patient received a number of treatments: baths, quinine extracts, camphor bromide, inhalation of amyl nitrate, leeches behind the ears, purgatives, and cold-water compresses on the head. Except for one day when she was more alert and able to get some gruel down, she was usually only able to choke down few drops of milk or wine. Her weight loss and decline were startling; on 5 May, Bourneville expressed astonishment that the girl was still alive ("*on ne conçoit pas comment elle peut vivre*"). She died the very next day, and the autopsy was performed on 8 May.

A painstaking macroscopic examination revealed the following. Brain weight was very low (1000 g), while the brainstem and cerebellum were of normal weight (150 g). The salient feature of the left hemisphere was "rounded, whitish, opaque islets of various sizes which formed part of but also protruded from the gyri; these protrusions were much more dense than the neighbouring tissue". In summary, he observed "a sort of hypertrophic sclerosis on large areas of the gyri" (Figure 2a). Sectioning these lesions revealed that they were solid. The next part listed the number and distribution of sclerosis lesions, which were plentiful throughout the left hemisphere, through less so in the right. No intraventricular lesions were visible, even in the basal ganglia, although the illustrations (credited, with thanks, to Bourneville's friend Brissaud) clearly show the typical line of subependymal nodules along the striatal sulcus (Figure 2b).

Bourneville found nothing remarkable about the organs, except for the kidneys. The right kidney weighed 70 g, "presenting on its surface three hard, white nipple-like structures 3 to 5 mm high; one of these masses has the volume of a hazelnut, and another, the volume of a walnut. There are also 15 other small, non-protruding nodules scattered across the two faces of the kidney. When sectioned, the main masses are similar in appearance to cancerous tissue. The left kidney had similar lesions, although there were fewer of them".

The discussion focused on the epileptic seizures, most specifically on those with focal onset on the right side of the body. Bourneville linked these to seizures described by Jackson and Charcot, considering them a form of complex evolving epilepsy, or 'hemiplegic epilepsy'. Despite the high seizure frequency, Bourneville did not believe the patient to be in grave condition as she regained consciousness between episodes and did not experience central hyperthermia. In the end, however, he recognised that there was little difference between his patient's condition and that of conventional status epilepticus with coma. In an attempt to correlate lesions with clinical symptoms, he posited that the large lesion on the ascending frontal and parietal gyri of the left hemisphere, which appeared to be fused, was the cause of the right-sided seizures.

Bourneville ended the discussion here without analysing the nature of the seizures, but stated that he would do so in a future study.

Subsequent cases

Bourneville's second publication on the neuropathology of idiocy, co-authored by Brissaud and published in the

same volume, included 'Observation V'.[4] This patient (George Bour—), also affected by both idiocy and epilepsy from the age of four months, was hospitalised in Bourneville's ward at the Bicêtre in June 1879, when he was four years old. He died on 6 January 1880, manifesting 'blue disease' caused by a heart malformation without neoplasia. The description of this patient's neurological symptoms was very brief owing to his extremely poor state of health due to heart failure. Despite this state of affairs, Bourneville continued to look after the child rather than giving up on him; as a minor triumph, he observed that the boy was able to walk again thanks to the care he received.

In the autopsy of this case, he described nodules on both hemispheres in great detail: "on the external wall of the lateral ventricles, there are numerous small sclerotic tumours measuring 2, 3, or 5 mm in diameter and grouped in clusters". A footnote warns readers that plate VII in this case study "is imprecise in that the illustrator has not depicted the sclerotic islets appearing along the striate body. A more precise idea of these lesions can be gathered by observing plate IV (in the previous section, 'Observation III') drawn with more care by M. Leuba" (Figure 2b). However, the original article cites Brissaud as the illustrator. Bourneville did not seem to have suspected that the cortical tubers and subependymal tumours, both of which were able to grow and become malignant, were different lesions; he describes both types as 'sclerotic islets'.

The third patient was Charles François Mor—,[5] who was institutionalised in the Bicêtre in January 1879 at the age of three. His parents and two siblings were

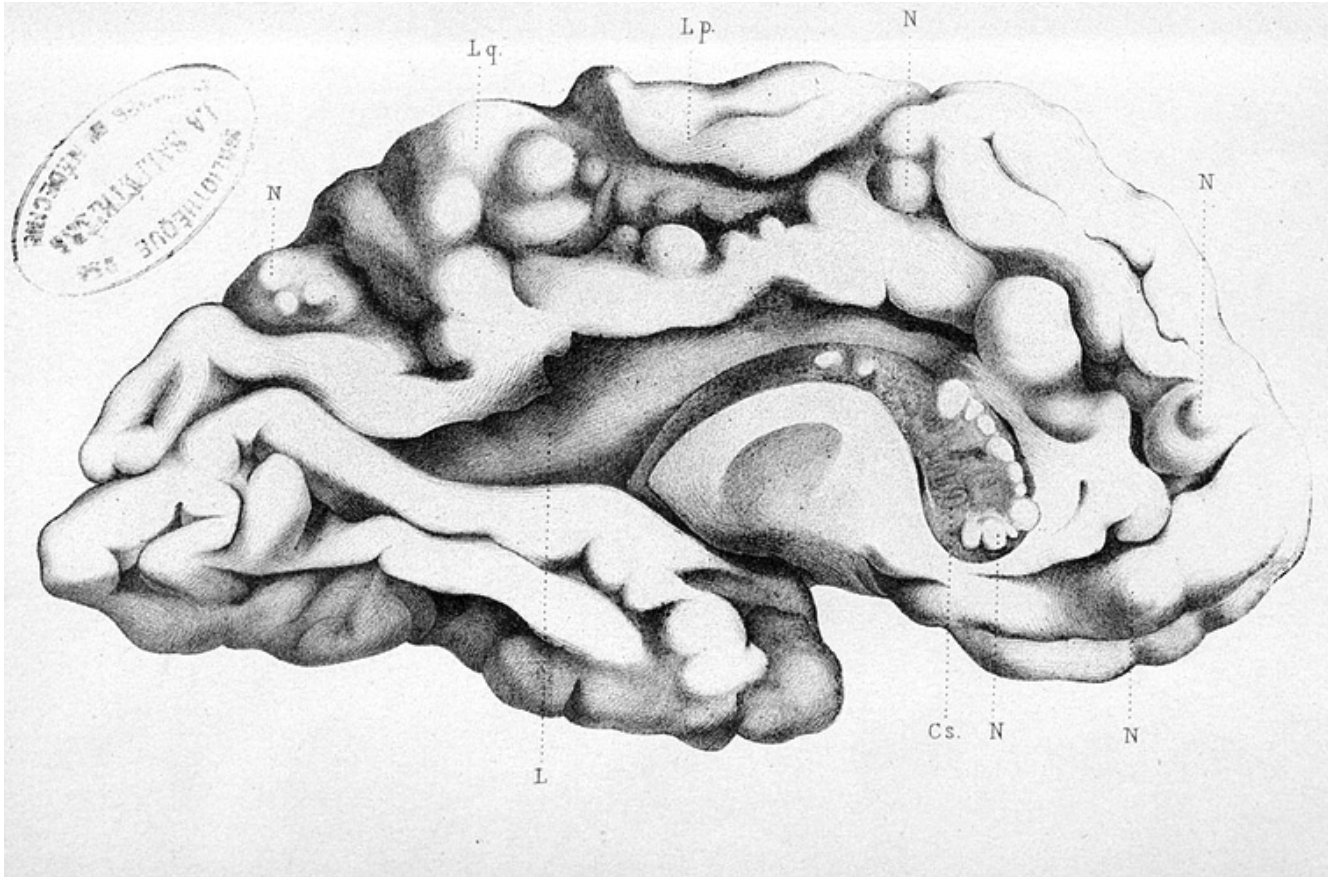

Figure 2. b) Drawing of the internal aspect of the same brain. In addition to some areas of cortical sclerosis, a line of subependymal nodules may be seen along the striatal sulcus. Fonds Charcot.

healthy, while he had experienced seizures with no distinguishing features from the age of seven and a half months. He displayed a total lack of speech and intellectual development, not even recognising his parents. He sucked his fingers constantly, occasionally shrieked, and experienced lip twitches. He died in January 1881 during an outbreak of rubella in the asylum. The autopsy report describes areas of cortical sclerosis in both hemispheres with subependymal nodules in the lateral ventricle. There were also renal tumours which M. Mayor examined with a microscope and described as 'encephaloid sarcomas'. The fourth case, a patient named Ernest Boru—, was five and a half when he was hospitalised in 1881. His parents and two older siblings were in good health, but he had experienced spastic seizures since the age of two months. He would later exhibit non-lateral tonic seizures, as well as an absence of psychomotor development. When he was admitted, he could stand only with assistance. He normally remained seated, swaying and making sucking motions, and he was also given to episodes of laughing, crying, or shouting at night. The patient continued to experience tonic seizures. He was described as having warts on his cheeks ("*productions de nature verruquese sur les joues*"). He died of a fever only a few months later. The autopsy revealed renal cysts and tumours. Areas of cortical sclerosis were described in both hemispheres, as well as tumours in the stria terminalis. By this point, Bourneville had seen four cases of the disease. His notes on these two patients are very brief. They simply list macroscopic and microscopic characteristics of the lesions, indicate that the disease is rare, and state that assigning a suspected in vivo diagnosis would be impossible because patients present non-specific and unremarkable signs of idiocy and epilepsy.

A few years would pass before Bourneville would present another case in *Recherches cliniques et thérapeutiques sur l'épilepsie, l'hystérie et l'idiotie*, part of the Bicêtre *Compte-rendu* for 1895 (published in 1896).[6] The introduction mentions two cases presented before the Anatomical Society, as well as J. Thibal's thesis (which Bourneville supervised) describing another case and mentioning earlier cases. At the time, case studies were often re-described and published several times.

Bourneville's new patient[6] was Leontine Laut—. Her medical history indicated that at about the age of three, she began to throw screaming fits, grind her teeth to the point of breaking them, and display episodes of generalised rigidity. She exhibited stereotypic behaviours including striking her head, rocking, mouth and facial contortions, biting her hands, and continuously stepping up and down onto the pavement. She was institutionalised at six years of age. She could walk and run, but was unable to speak or eat on her own. She did not display affection toward her mother or play with other children, but she was able to amuse herself for hours with noise-making objects. Her stereotypic behaviours and attacks of rage persisted. An examination revealed an "erythematous rash at the base of the nose and reddish freckling across the face, especially on the left cheek". He provides a very detailed description of small scars from injuries or vaccinations without any mention of achromic or shagreen patches, although he does characterise the skin of her torso as 'roughened'. A conventional neurological examination delivered normal findings. The patient died on 30 July 1895. While the brain autopsy listed hypertrophic sclerotic lesions of the gyri, it did not describe any on the ventricular wall. Bourneville regretfully states that the autopsy was performed while he was away at a congress in Bordeaux and was left incomplete. In this case, his neuropathological characterisation is hard to decipher. On the one hand, he mentions the cortical nodules found in tuberous sclerosis, while on the other, he states that the parts of the gyri without nodules were affected extensively by 'meningoencephalitis'. The description, however, does not match that of an infectious or inflammatory process. He later reflects on the aetiology and nature of the disease and on its clinico-pathological correlations. Following in the footsteps of Charcot, he stressed the importance of 'inheritance'; the child's father had died of neurosyphilis, and the mother, likewise affected, had suffered multiple miscarriages before the patient's birth. He refrains from stating whether the convulsions are a cause or a consequence of tuberous sclerosis, and this lack of a position clashes with the conclusions he had reached in previous articles. Instead, he attributes 'episodes' of shouting, head-striking, tooth grinding, etc. to 'cortical meningoencephalitis'.

Bourneville's next report was dated 1899.[7] This seventh case was detected in Angéle Blach—,[7] born on 14 April 1894 and institutionalised on 12 February 1896. She died in 1897. Her family history was unremarkable; the child was raised by a wet nurse and her development until the age of six months was considered normal. Convulsions began around that time, but no further

details were known. The child's development halted, and when she returned to her parents at ten months, she was no longer normal. Her epileptic seizures were described as brief, tonic episodes of generalised rigidity, sometimes occurring in clusters; she also exhibited shouting, tooth grinding, and rocking episodes. The patient never showed any signs of intelligence. A painstaking description of her physical features depicted no marks or rashes on her face and no anomalies of her teeth or fingernails. Results from the neurological examination were within normal limits. In the months after she was institutionalised, her condition improved and she grew closer to her carers. The epileptic seizures continued and their numbers were recorded every month (range, 0 to 23). The patient died of a bout of diarrhoea. The autopsy found only brain lesions, whose macroscopic appearance was that of classic tuberous sclerosis. The novel aspect of this article is

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NOMS.	Age.	Sexe.	DIAGNOSTIC.	NATURE DES CRISES.
Pit.....	15 ans.	F.	Idiotie, épilepsie hémiplégique.	Accès et vertiges
Bour.....	5 ans.	G.	Idiotie, épilepsie, maladie bleue.	Id.
Mar.....	4 ans.	G.	Idiotie, épilepsie.	Id.
Caill.....	21 ans.	G.	Idio., épil. procursiv.	Accès.
Boull.....	5 ans 1/2.	G.	Idiotie, épilepsie.	Id.
Lauti.....	6 ans.	F.	Idiotie.	Ni accès, ni vertiges.
Blanch.....	3 ans.	F.	Idiotie, épilepsie.	Pas d'accès, Vertiges.
Bertra.....	16 ans.	F.	Imbécillité, épilepsie.	Accès et vertiges
Pier.....	9 ans 1/2.	G.	Idiotie, épilepsie.	Ib.
Grosma	14 ans.	G.	Idi. épil., paraplégie.	Accès.

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MÉNINGO-ENCÉPHALITE.	BIBLIOGRAPHIE.	CAUSES DE LA MORT.
s de méningo-encéphalite.	*Archives de Neurologie* t. I, 1880-1881, p. 81.	Série d'accès, pneumonie.
Id.	*Comp.-rendu*, et *Progrès Médical*, a. 1880-1881, nº 9, p. 1. *Archives de Neurologie* t. I, 1880-1881, p. 397.	Maladie bleue, pneumonie.
Id.	*Progrès-Médical*, a. 1881. p. 667. *Société anatomique*, 1881, p. 180.	Rougeole, bronchopneumonie.
Id.	*Thèse Thibal*, 1880, p. 57.	Pleurésie enkystée.
Id.	*Progrès Médical*, 1881, p. 100 et 545. *Société anatomique* a. 1881.	État de mal.
Méningo-encéphalite.	*Compte-rendu*, de 1895, p. 98.	Tuberculose, pulmonaire, cachexie.
Méningo-encéphalite.	Voir plus haut, p. 183.	Entérite
Id.	Inédite.	État de mal.
Id.	Inédite.	Tuberculose généralisée.
Id.	Inédite.	Cachexie et tuberculose.

Figure 3. Summary of the ten cases with tuberous sclerosis reported by Bourneville. *Archives de Neurologie*. Fonds Charcot.

that it includes a modern histological study conducted by C. Philippe in which blocks from the patient's occipital lobes were embedded in celloidin and stained with alum haematoxylin, Weigert-Pal-Kolschitzky haematoxylin (myelin and nerve fibres), and picroindigocarmine. Cortical lesions were focal in both grey and white matter and interspersed with normal cortical areas. In sclerotic foci, the lesion 'intensity' also varied; some still contained neurons, while others did not and had only a dense network of neuroglia remaining. On this basis, sclerotic foci were classified as 'maximum', 'intermediate', and 'initial'. Glial fibres are the most dense around blood vessels and on the pial surface, where they form swirls (*tourbillons*). The most fascinating histological detail is the description of "large cells measuring 40-60 microns, with very abundant protoplasm...without pigment or granular matter...when stained with picrocarmine". Bourneville believed these cells to be glial in origin, and they were most likely the characteristic balloon cells of cortical tubers. Whether these are neuronal or glial has been debated for decades in modern neuropathology.

Lastly, the article presents a series of reflections. In this case, a family history of diseases such as syphilis or alcoholism was lacking. Bourneville believed that the child was developing normally until her seizures started at the age of six months, and these events were the cause of her mental retardation. However, in another of his remarks he appears to consider sclerosis as the causal agent of both the idiocy and the seizures. And yet again, Bourneville mentions 'meningo-encephalitis' as the lesion associated with sclerosis, and finds it responsible for all the other clinical manifestations, including tantrums, shouting fits, tooth grinding, and so on. As proof of his profound commitment to child welfare, he does not neglect to mention that during the patient's stay at Fondation Vallée, despite her poor condition, her carers witnessed 'relative improvement' in her attention span, reactions, personal relationships, and gait.

This last patient was Bourneville's tenth observed case, and he provided a summary in table format (Figure 3). The mean age of the patients was 8.9 years (range, 3-21). Their number comprised four girls and six boys; cause of death was status epilepticus in two cases and a variety of infectious diseases in the rest. Most of the children were diagnosed with idiocy and epilepsy; one was affected by idiocy alone (Laut—), and another case was described as 'imbecile, epileptic'. Seizures were classified as *accés* and *vertiges*. Except for the case of Laut—, who experienced no seizures, six children had both types, two had *accés* seizures, and one had *vertiges* alone. Neuropathological findings described as 'meningo-encephalitis' were present in all the children. The first six cases had already been published, one of them as Thilal's thesis. Bourneville provided the bibliographical references for all of them.

Bourneville published the last case in 1900.[8] In this article he reports the symptoms described previously, and the patient, Henri Grosma—, who was born in 1885 and institutionalised in 1898. The patient's records indicated "idiocy with very frequent epileptic-like seizures, no signs of intelligence, complete lack of articulate language, numerous malformations, and paraplegia with abnormal foot position". The mother recounted: "my brother, who had an eczema...had a child who died at the age of 19 months. The baby showed no signs of intelligence, just like my son". Before Henri Grosma—, his mother had given birth to two other children, who had seizures and died at the ages of five and seven months, respectively. Henri had very frequent seizures starting when he was three months old. His limbs contracted at the age of two years. The patient never learned to sit down or articulate a word, or in fact showed any signs of intelligence. He died of tuberculosis in April 1899. After performing the brain autopsy, Bourneville thoroughly described cortical tubers in both hemispheres and concluded by highlighting the presence of two findings that seemed to be a constant in those patients: the line of subependymal nodules along the striatal sulcus, and the renal tumours ("*Notons pour memoire, les trainées de nodosités sclereuses des ventricules latéraux et les petits neoplasmes des reins, lésions qui sont constantes*"). However, he did not hypothesise about the significance of these findings.

Discussion

The nature of the disease

It was in his second article[4] that Bourneville discussed the possible nature of these "morbid findings that seem to represent a new disease" since "no examples have been reported in the neuropathology literature". There is no doubt that Bourneville was not informed of the purely anatomopathological description published by Von Recklinghausen, who had previously described the case of a newborn with cardiac tumours and sclerotic lesions in the brain but had provided no clinical description.[9] He

reviewed the literature in search of a connection between sclerosis and epilepsy, indicating that Hoffman "performed autopsies on several patients with epilepsy and had found that the frontal gyri, especially in the grey matter, had a cartilaginous consistency". However, he did not use these cases as a basis for his discussion since he did not have enough information to definitely connect them. Finally, regarding the pathogenesis of the disease, Bourneville noted that sclerosis was more intense on the surface of the nodules while no alterations were seen in the meninges, and therefore ruled out the hypothesis that the disease might be secondary to some type of meningitis. He stated: "This entity is more of a disease of the brain surface than of the cortex itself". Bourneville discarded the idea that tuberous sclerosis was secondary to meningitis, and described it as a "slow chronic inflammatory process originating in the glia of cortical grey matter". Hence, he used the terms 'meningo-encephalitis' (Figure 3) and 'tuberous encephalitis' in subsequent articles.

A retrospective analysis of Bourneville's ten cases draws attention to several facts. Only the first case presented cutaneous lesions on the face. Although the description of these lesions did not correspond to typical angiofibromas, they had the same distribution pattern and had already been described.[10] Bourneville described warts on the cheeks of Boru— and an "erythematous rash at the base of the nose and reddish freckling across the face, especially the left cheek" in the case of Laut—. Although none of these findings was seen in the patients' parents, the uncle of Henri Grosma— was reported to have eczema as well as a child with idiocy and epilepsy.

It is well known that the rate of new mutations for this disease is very high (50%-70% according to different series)[11]; however, we also know that manifestations in carrier parents may be minimal and can only be detected after conducting a thorough study. As there were no clinical data clearly indicating the heritability of the disease, it is not surprising that Bourneville did not suspect the genetic nature of it, even though inheritance was an important aetiological factor of Charcot's teachings. We should bear in mind that, at that time, the concept of inheritance was not linked to what we currently know as the genome, but was rather associated with lifestyle. Mental retardation and epilepsy in a child were attributed to 'inheritance' if the father was alcoholic and abused his wife when he was intoxicated.

It is striking that no achromic or shagreen patches were mentioned considering the thoroughness of the clinical examinations and autopsies. The mean age of these patients was 9 years; at that age, nearly all of them displayed hypomelanotic macules, around 70% displayed facial angiofibromas, approximately 60% renal tumours, and 20%-30% rhabdomyomas.[11] Interestingly enough, Bourneville found tumours in all the patients in his series but none of the other typical clinical lesions, despite examining each case in great detail.

His description of epileptic seizures does not coincide with any of the epileptic syndromes we know today, except for those of the first patient, whose brief seizures "affecting mainly the head while the limbs bent forward" may be interpreted as spasms in late-onset West syndrome. Blach— was described as normal until the age of six months, when epileptic encephalopathy halted her development; when the patient was ten months old, she already displayed severe mental retardation. Her age and the neuropathological substrate of the disease suggest West syndrome, but with what we know of her medical history it is impossible to objectively confirm this diagnosis. Bourneville's comments indicate that he believed that seizures in and of themselves worsened the patients' state of health. The terminology of the time is of little help in interpreting seizures: although they were classified as '*accés*' or '*vertiges*', the semiological differences between these two types have never been clearly defined.

As would be expected considering the setting, all the cases described by Bourneville presented a profound mental retardation. In fact, this was without exception the cause for institutionalisation. We now know that the disease is associated with an extraordinarily variable phenotype, and patients with abundant cortical tubers may in fact display average intellectual functioning. Had Bourneville realized this, he would have delighted his teacher Charcot, who was so keen on describing the *formes frustes* and varieties of all types of neurological diseases.

Autistic behaviour is one example of the wide range of clinical manifestations of tuberous sclerosis. Patient descriptions did not give a detailed account of behaviour, although they did mention stereotypic behaviours such as hand sucking, clapping, and isolation tendencies, as in the case of Laut—. In addition to stereotypic motor behaviours, this patient was reported as not displaying affection toward her mother or playing with

other children, although she did amuse herself playing with objects that made noise.

Tuberous sclerosis and the neuropathogenesis of idiocy

When Bourneville reported the first case of tuberous sclerosis,[2] he provided a pathological description of the disease but did not hypothesise about its nature, which is surprising considering the novelty of his findings. Publishing several articles about the same research was common at that time. Bourneville announced that he would discuss the pathogenesis of the disease in a subsequent article, co-authored with Brissaud, although he did not explain the rationale behind his decision. Undoubtedly, this means that Bourneville had experience with at least one other case when he published the first article.

The autopsy of the first case (Observation III) was performed in May 1879 and the article on it was published in the first issue of *Archives de Neurologie* in July 1880. It is therefore to be expected that by the time that the first case was published, Bourneville already knew the results of the autopsy of the second patient (Observation V), who was institutionalised in 1879 and died in January 1880, and whose case was published that same year in *Archives de Neurologie*. This suggests that leaving the discussion of the pathogenesis of the disease for a subsequent article was deliberate, since he already had another confirmed case to support his hypothesis. At the same time, presenting one case at a time may well be a smart move on the part of the publishers in order to maintain the interest of the public.

Speculations aside, let us now address the impact that publishing his observations had on Bourneville's career. When he observed the first case in 1879, Bourneville was no longer a young resident. He was nearly 40 and about to be appointed head of the boys' ward at the Bicêtre, and he was already active in politics.[1,2] Bourneville was deeply committed to implementing major reforms in education and healthcare. One may well wonder why such a busy man would take the trouble to examine, treat, write the clinical histories, and perform the autopsies of these 'idiot children'. What was the driving force behind his efforts?

There is no question that his motivation was a determination to fight the idea that idiocy was untreatable, at that time a widespread belief that had passed down from Esquirol.[13] The reason why Bourneville devoted many years to studying the clinicopathological correlations of idiocy despite being in his forties and already having a great deal of responsibility, was to prove that this disorder was not an irreversible disease state per se, but rather the result of a wide range of pathological processes that could be studied, treated, and even prevented, like any other disorder. This explains his presentation at the neurology section of the International Congress of Medicine in Paris in 1900 which was titled '*Anatomie pathologique de l'idiotie*'.[14] According to the records, his participation was a true *leçon des choses*: for each pathological finding, Bourneville provided "two or three brains and their craniums, several pictures of those brains, and pictures of the patients, which were taken every two years from institutionalisation till death". As a result, he established ten different types of idiocy, some of which have great significance, such as mongolism and 'pachydermic cachexia' (myxedema and hypothyroidism).

Without his valuable clinicopathological contribution to knowledge about idiocy, it seems unlikely that Bourneville would have been credited for his tireless efforts to do nothing less than reform the boys' ward and turn it into a praiseworthy and modern medical-pedagogic institute. Coherence and consistency seem to have been key to Bourneville's successful endeavours. As Poirier and Chretien point out,[15] for Bourneville "a republican —that is, a freethinker and a progressive— and a doctor embody the same ideal".

Conflicts of interest

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