The hyperkinetic child –
Moving forward by looking back

215 years ago, the Scottish physician Alexander Crichton presented cases of children who exhibited attention deficits, hallmarks of a disorder today known as attention deficit-hyperactivity disorder (ADHD), one of the most common childhood onset psychological problem.

Since that time there has been a fascinating history of clinical and basic research on ADHD symptomatology: research into its clinical features and subtypes, disorder-specific aspects of social interaction, the course from childhood to adulthood and gender differences, non-genetic and genetic etiologies, the association with brain structure and cerebral functioning, the relevance of neurotransmitter systems, research concerning developmental comorbidity and quality of life and investigations of treatment approaches, including psychotherapeutic and psychopharmacological research.

In this illustrated brochure, we have compiled some chapters which briefly summarize the main steps of this fascinating history on ADHD-associated research. We have put a special focus on topics with rich graphical material and are therefore especially indebted to the Struwwelpeter-Museum, the Emma Pendleton Bradley Hospital and the Firmenarchiv Novartis AG for providing photos and illustrations from their vast archives.

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We hope you enjoy this history!


The authors can be reached at criederer@email.de, and welcome suggestions and ideas!
Part I

The idea of "uncontrolled" behaviour as a medical problem
While stories of restive and undisciplined children are as old as humanity itself, reports of fidgety and restless children in a more closely medical context can be traced back at least as far as 1798, when the Scottish-born physician and author Alexander Crichton (1763–1856) described in his book *An inquiry into the nature and origin of mental derangement* a mental state reminiscent of the inattentive subtype of ADHD. In this work, he observed clinical cases of mental illness and dedicated a chapter “on attention, and its diseases.”

“The incapacity of attending with a necessary degree of constancy to any one object, almost always arises from an unnatural or morbid sensibility of the nerves, by which means this faculty is incessantly withdrawn from one impression to another. It may be either born with a person, or it may be the effect of accidental diseases. When born with a person it becomes evident at a very early period of life, and has a very bad effect, inasmuch as it renders him incapable of attending with constancy to any one object of education. But it seldom is in so great a degree as totally to impede all instruction; and what is very fortunate, it is generally diminished with age.”


A few years later, in 1809, the English physician John Haslam (1764–1844) provided the case history of a ten year old boy who was “the creature of volition and the terror of the family”, or, in brief, a destructive lad with uncontrollable impulsivity.

“At the age of two years, the subject of the present relation, became so mischievous and uncontrollable, that he was sent from home to be nursed by his aunt. In this situation at the request of his parents, and with the concurrence of his relation, he was indulged in every wish, and never corrected for any perverseness or impropriety of conduct. Thus he continued until he was nearly nine years old, the creature of volition and the terror of the family.”

Haslam, 1809, p. 199f.
Some more observations

At about the same time, in 1812, the multi-talented American Benjamin Rush (1745–1813), among whose achievements was the signing of the Declaration of Independence, added his observations on uncontrollable children and adults and speculated on the “defective organization in those parts of the body which are occupied by the moral faculties of the mind.”

“...and directing their attention, and this privation is the primitive cause of all their errors. We observe this among children, who, although very impresible, have nevertheless few sensations, for want of attention.”

Esquirol, 1845, p. 28f.

Valuable observations in the 19th century were also made by the famous French psychiatrist Jean-Étienne Dominique Esquirol (1772–1840) and by the British psychiatrist Henry Maudsley (1835–1918), who in his book The physiology and pathology of the mind (1867) described a child “driven by an impulse of which it can give no account, to a destructive act, the real nature of which it does not appreciate: a natural instinct is exaggerated and perverted by disorder of the nerve centre, and the character of its morbid manifestation is often determined by accidents of external circumstances.”

“In the course of my life, I have been consulted in three cases of the total perversion of the moral faculties. One of them was in a young man, the second in a young woman, both of Virginia, and the third was in the daughter of a citizen of Philadelphia. The last was addicted to every kind of mischief. Her wickedness had no intervals while she was awake, except when she was kept busy in some steady and difficult employment. In all these cases of innate, preternatural moral depravity, there is probably an original defective organization in those parts of the body, which are occupied by the moral faculties of the mind.”

Rush, 1812, p. 359f.
Thomas Smith Clouston (1840–1915) was a notable Scottish psychiatrist of the late 19th century who wrote prolifically on the nature of mental illness and theories of treatment. For most of his career, he served as physician superintendent at the *Edinburgh Royal Asylum*.

In 1899, Clouston published a remarkable article on states of over-excitability and mental explosiveness, in which he described cases of impulsive children with learning problems. He outlined a therapy consisting of individual dietary and social treatments, including environmental improvements, and a pharmacological intervention consisting of carefully dosed grains of potassium bromide.

The Scottish Medical and Surgical Journal

*States of over-excitability, hypersensitivity, and mental explosiveness in children, and their treatment by the bromides*

By T.S. Clouston, M.D., F.R.C.P.Ed., Physician Superintendent Royal Edinburgh Asylum, and Lecturer on Mental Diseases in the University of Edinburgh

“I do not advocate bromide treatment alone [...] I think milk will be found the sheet anchor in dieting all such neurotic children. Environment too, fresh air, suitable amusements, companionship, control, employment must be looked to, and the schoolmaster must be regarded for the time as an aid to treatment and so under the doctor’s order.”

T.S. Clouston, 1899.
While working at King’s College Hospital in London, George Frederic Still (1868–1941) presented a series of three lectures on March 4, 6 and 11, 1902 to the Royal Society of Medicine in London, the Goulstonian Lectures on "some abnormal psychical conditions in children", which were also published in April 1902 in the Lancet. In these lectures, Still described the cases of 23 examined children from his practice, aged between three and twelve years, who showed diminished “moral control”, were excessively passionate and emotional, and had problems at school. As these children came mainly from normal families and had no general impairment of intellect, Still concluded that the underlying cause of the defect was some morbid physical condition. He described a number of diseases that might be responsible, and also linked the moral defect to morbid nervous and mental conditions.

„Another boy, aged six years, with marked moral defect was unable to keep his attention even to a game for more than a very short time, and, as might be expected, the failure of attention was very noticeable at school, with the result that in some cases the child was backward in school attainments, although in manner and ordinary conversation he appeared as bright and intelligent as any child could be."

Still, Goulstonian Lectures, Lecture III.

Some abnormal psychical conditions in children: The Goulstonian Lectures of 1902.

Lecture 1 held on March 4, published on April 12.
Lecture 2 held on March 6, published on April 19.
Lecture 3 held on March 11, published on April 26.

The Goulstonian Lectures are named for the English physician Theodore Goulston (1572–1632).
Alfred Tredgold (1870–1952), a highly respected member of the English Royal Commission on Mental Deficiency and author of Mental Deficiency (Amentia; first published 1908), extended Stills’ theory and observations and suggested that some forms of brain damage could present as behaviour or learning problems in early school years. He was also the first to propose the existence of what would later be termed “minimal brain damage”.

Tredgold and Still were well aware of the legal and social importance of their findings. While the initial clinical description of ADHD is usually attributed to Still, Tredgold’s writings had a lasting impact on the social and political debate at the beginning of the 19th century on how to deal with the feeble minded, as well as upon the classification of mental disorders through the landmark Mental Deficiency Act of 1913. As attendance at public elementary and other schools had been compulsory in England since 1876, Tredgold and other researchers had access to a vast set of data and reports, but it was some time before effective management of these children was developed.

"Attention – In the lethargic, inert type of feeble-mindedness there is a defect of spontaneous attention; but this is never so marked in this degree as in the more serious grades of amentia. The general stir and excitement aroused by a visitor is much more pronounced in the special school than in the imbecile ward. On the other hand, active or voluntary attention is commonly in defect, both with regard to its intensity and its duration. The most trifling thing serves to distract these children from their occupation, so that even where the attention is readily gained, it is with difficulty held. Many of them become capable of pursuing a congenial task with a certain amount of patience, but the majority have neither power of concentration nor will sufficient to be capable of sustained mental effort against inclination or interposed obstacles. They must go with, for they cannot fight against, the stream; and this lack of willpower and driving force is one of the most distinguishing characteristics of aments at all ages."

Alfred Tredgold, Mental Deficiency, 4th edition, 1922.
"Brain damage" and behaviour disorder

Between 1917 and the late 1920s, encephalitis lethargica was an epidemic and often lethal neurologic disease. In adults, it typically elicited severe somatic effects, and in particular, various forms of cranial nerve and motor dysfunction. In children, the psychiatric effects were often as severe as the physical consequences. Approximately one third of affected children underwent a rapid transformation from normal behaviour to impulsiveness, emotional lability, precocious sexuality, self mutilation, a tendency to wander, and delinquency, often to a degree requiring confinement in psychiatric or penal institutions. The onset of the final and largest epidemic in 1924 caused a great deal of public and political concern caused by "a disease which makes criminals" (The Times, London, August 20, 1924). Encephalitis lethargica was cited in the defence of youths arraigned for various crimes during the 1920s, and its effect on adolescents was the subject of parliamentary debate and government enquiries. Special institutes for the care of such children, with varying success, were established in various countries, including Germany, France, the United Kingdom and the United States. Many neurological and psychological theories were advanced to explain these severe behavioural changes, and the therapeutic approaches employed ranged from training in dedicated schools to frontal leukotomy. Neither intelligence nor memory were consistently impaired in the disorder, but concentration and sleep were commonly affected: the children tend to be overactive through the night but slept through most of the day. Doctors also noted that although children suffering post-encephalitic psychiatric disturbances could exhibit the cruelest behaviour – for example, removing their own eyes or killing a sibling – they exhibited genuine remorse after the fact, and claimed to have been compelled to act as they did. The link between the approximately contemporaneous "Spanish" influenza epidemic and encephalitis lethargica remains unclear, but it is possible that influenza played a direct or indirect role in the etiology of the disorder. Encephalitis lethargica triggered behavioural changes in children that are not duplicated by any other neurologic condition, with the possible exception of traumatic brain injury. The ultimate fate of such children could hardly be more tragic: their behavioural problems receded during their early 1920s, only to be replaced by rapidly advancing parkinsonism from which there was no recovery.

By Paul Foley, Sydney, Australia.

Articles of Ebaugh (1923) and Stryker (1925) describing behavioural consequences of encephalitis in children.
Alongside the protagonists of the Second Viennese Medical School, Theodor Meynert (who described the basal nucleus named for him) and Julius Wagner-Jauregg (Nobel laureate 1927), the cosmopolitan Constantin von Economo (1876–1931) made significant contributions to neuroscience.

He was born in Romania, the son of a wealthy Greek family who later moved to Trieste and finally settled in Vienna where von Economo spent most of his academic career, although he studied some years abroad in Munich, Berlin and at La Salpêtrière in Paris. Among his teachers were some of the most prominent scientists of the beginning 20th century, Alois Alzheimer, Emil Kraepelin, Hermann Oppenheim, Theodor Ziehen, Pierre Marie and Fulgence Raymond.

His own masterpiece was the seminal description of encephalitis lethargica in 1917, including accounts of the neuropathological basis and its clinical spectrum. Subsequent work explored its role as a major trigger of postencephalitic parkinsonism as its late sequela. Von Economo made also important contributions to the cytoarchitecture of the cerebral cortex and sleep regulation and served as military pilot in WW1.
Part II
Towards the concept of ADHD
Towards terminology

In the 19th century, behaviour problems, uncontrollability and impropriety of conduct as medical problems were associated with morbid nervous conditions, brain damage and brain dysfunction. This emphasis on biological factors continued in the early 20th century in the works of George Frederic Still and Alfred Tredgold, who claimed that forms of brain damage were involved, an argument brought forward in the 1930s and 1940s, too, particularly in the publications of Alfred Strauss and co-workers who coined the term “brain-injured child”. This terminology reflected the assumption that some injury is the cause of behaviour disturbances, but it was called into question when further research examined the causes of behaviour problems in childhood and a shift towards psychological factors occurred.

Such observations on social milieu and life quality were made as early as 1935 by A.T. Childers and ultimately gained ground in the 1970s and 1980s with the works of Virginia Douglas, from the McGill University in Montreal. Douglas argued that the major disability of hyperactive children involved an inability to sustain attention and to inhibit impulsive responding during tasks and situations requiring organized and focused efforts.
Another strong input throughout most of the 20th century was the concept of hyperkinesia, culminating in the work of Kramer/Pollnow, and further investigated by Maurice Laufer and Stella Chess. Laufer and co-workers described the “Hyperkinetic Behavior Syndrome in Children” and the “Hyperkinetic Impulse Disorder” in 1957, while Chess published an influential article in 1960 in which she presented her experiences with hyperactive children as well as therapeutic options.

Reflecting this thought, the disorder was mentioned in the 2nd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM II) in 1968 as the “hyperkinetic reaction of childhood”, then “attention-deficit disorder” in DSM-III (1980), and “attention-deficit/hyperactivity disorder” in DSM-III-R (1987) and DSM-IV (1994). The most recent edition (DSM-V, 2013) will not make vital changes on the diagnostic concept, but relevant modifications include the age of onset, the symptomatic threshold for adults, and the removal of autism spectrum disorder from the exclusion criteria. In the WHO manual, the disorder was labeled as “hyperkinetic reaction of childhood” in ICD-8 (1974) as well as “hyperkinetic syndrome” (ICD-9) and “hyperkinetic disorders” (ICD-10), the latter term including subtypes of ADHD.
Heinrich Hoffmann was born in Frankfurt/Main, Germany, the son of the architect Jacob Hoffmann and his wife Caroline née Lausberg. His mother, who belonged to the upper class, was in poor health and died in 1810, when Heinrich was only six months old. Three years after her death, Jacob Hoffmann married her sister, Antoinette Lausberg. Hoffmann described her as a loving mother to him and his two step-sisters, Sophie and Berta. Hoffmann left a versatile life’s work, as a citizen of Frankfurt, as a children’s author, as a writer of poems and satires, as a psychiatrist, and as a family man. Hoede and Bauer characterized Hoffmann’s life as lying between “wit and delusion.”

In 1816 Hoffmann was enrolled in school, and during his elementary school years was tormented by some of his classmates. He was said, on the one hand, to be a feeble and anxious child, but also, on the other, lively, talkative, funny and inventive. It is also reported that he hardly took school seriously until tertiary level, and that he was initially a rather lazy and distracted pupil. In 1828, he finished high school with the German Abitur. From 1829 to 1832, Hoffmann studied medicine in Heidelberg, then continued his studies in Halle, where he obtained his doctorate. He then lived in Paris for a few months. When his father fell ill and died, the young doctor returned to Frankfurt and settled as general practitioner and obstetrician. Some doctors in Frankfurt had founded a clinic for the poor and underprivileged that Hoffmann later joined. In 1840, Hoffmann married Therese Donner; their son Carl Philipp was born a year later, but died young in 1868 in Peru. Their daughter Antonie Caroline (Lina) was born in 1844; her husband later left her a young widow, and she and her children moved into her father’s house until she died. The third child, Eduard, born in 1848, was very successful, but remained single and childless.
Hoffmann was a creative personality who wrote poetry and sketched pictures throughout his life, not only for publication. His first and most famous book, "Slovenly Peter" ("Struwwelpeter"), has been translated into almost all languages of the world. Hoffmann could not find a suitable gift for his son Carl in the bookstores of Frankfurt, so he originally designed the small book as a Christmas present in 1844. The picture book includes a series of self-contained, illustrated stories that warn against the devastating consequences of disobedience and wickedness. "Slovenly Peter", for example, willfully and defiantly refused to have his hair and nails cut for a year. Unkempt, and thus offending all the rules of personal hygiene, he finally stands defiantly on his podium, labeled by others an outsider. The next tale recounts "The Story of Bad Frederick", who is very impulsive and aggressive: he tortures animals and people, until he is finally injured by a resisting dog. While the dog enjoys thereafter the amenities of Frederick’s life, he must remain in bed. "The Dreadful Story of the Matches" warns of the dangers of fire: Paulinchen ignores the warnings of two cats and the prohibition of her parents, and plays with matches while at home alone, and is ultimately burned to death. "Fidgety Philip", the most cited story in the context of ADHD, exhibits a restlessness that is a burden on family life. The plight of the parents becomes apparent when Philip once more "flutters", "rocks", "fidgets" and "clatters" at table: in their helplessness, they react with anger.
In "The Story of Johnny Head in-Air", a dreamy, distracted and inattentive child is described, who ends up falling into the water he has not seen before him. The book was not only acknowledged immediately after its publication by loud applause, but was also subject to fierce criticism directed against the terrifying images, the cruelty of the punishments, and the underlying pedagogic concept, described as "repressive and impatient" (Tresnak, 2005). However, Hoffmann’s work can only be seen in the context of bourgeois society with its strict moral notions and civic values that specified how a well-behaved child was to behave. The behavioural patterns probably depict precursors of mental disorders in children such as anorexia, disorders of social behaviour, and hyperactivity. However, the stories lack background and do not explain why the children acted in evil, dangerous or naughty ways. The book shows no evolution and no explanations are sought or supplied. The book explains neither why Frederick becomes so aggressive, why “Slovenly Peter” is not willing to have his hair cut, nor why “Soup-Kaspar” refuses to eat his food. For this reason, no detailed depiction of mental disorders by the book can be derived. It might nevertheless be asserted that Hoffmann was among the first authors who addressed behavioural disorders in children and adolescents.

Drawing of the front page by H. Hoffmann and various covers of international editions of the "Struwwelpeter", contributed by the Struwwelpeter-Museum, Frankfurt, Germany.
Hoffmann felt comfortable as a physician, especially as medical director of the "lunatic asylum." Prior to 1851, when he commenced as physician at the Frankfurt "Asylum for the Insane and Epileptic", he had never set foot in a "lunatic asylum", but quickly showed that he was the right man in the right place. As usual in the mid-19th century, Hoffmann and his family lived in the hospital and he was in permanent contact with his patients and responsible for their daily care. He attempted to apply the latest advances in psychiatry and managed to introduce proper employment, reasonable nutrition, and humane treatment, as well as orderliness and cleanliness. From 1851 to 1852 Hoffmann undertook several trips to visit other European "lunatic asylums" and became convinced that conditions for the mentally ill in Frankfurt were unacceptable. He successfully organized a huge crusade to motivate citizens to donate money for a new "asylum" in Frankfurt which finally opened in Frankfurt’s Westend in 1864.

"...when a physician enters a hospital department, it should have some traits of a sunrise, it must spread warmth and light; and so it should be in every patient’s room."

Hoffmann also warned: "What you cannot give the patient through your knowledge and art, try to give through emotional participation and love."

Advice of Hoffmann for fellow doctors on the occasion of his 50th anniversary as physician in 1883, quoted in Siefert and Herzog-Hoinkis, 2009, p. 108f.

All texts by Siebke Melfsen and Susanne Walitza, Zurich, Switzerland.
Photos and pictures contributed by the Struwwelpeter-Museum, Frankfurt, Germany.

The Story of Fidgety Philip

Let me see if Philip can
Be a little gentleman
Let me see if he is able
To sit still for once at table:
Thus Papa bade Phil behave
And Mamma looked very grave
But Fidgety Phil
He won’t sit still
He wriggles
And giggles
And then, I declare
Swings backwards and forwards
And tilts up his chair
Just like any rocking-horse-
"Phil! I am getting cross!"

See the naughty, restless child
Growing still more rude and wild
Till his chair falls over quite
Philip screams with all his might

Catches at the cloth, but then
That makes matters worse again
Down upon the ground they fall
Glasses, plates, knives, forks, and all.
How Mamma did fret and frown
When she saw them tumbling down!
And Papa made such a face!
Philip is in sad disgrace

Where is Philip, where is he?
Fairly covered up you see!
Cloth and all are lying on him
He has pulled down all upon him
What a terrible to-do!
Here a knife, and there a fork!
Philip, this is cruel work
Table all so bare, and ah!
Poor Papa, and poor Mamma
Look quite cross, and wonder how
They shall have their dinner now.

"...when a physician enters a hospital department, it should have some traits of a sunrise, it must spread warmth and light; and so it should be in every patient’s room."

Hoffmann also warned: "What you cannot give the patient through your knowledge and art, try to give through emotional participation and love."
Kramer and Pollnow worked together at the psychiatric and neurological hospital at Berlin’s Charité under Karl Bonhoeffer, a renowned psychiatrist who led Germany’s most prestigious and influential clinic from 1912 to 1938. In view of the rising number of hospitalized children, Bonhoeffer had opened a special ward dedicated to the observation of children in 1921 and appointed Kramer its head. Similar wards were opened at that time throughout Berlin and in other German cities, a development that was pioneered by the famous paediatrician August Homburger (1873–1930) in Heidelberg, who opened one of the first centers where parents could seek advice on psychiatric matters affecting their children.

Another leading figure at the Charité was Adalbert Czerny (1863–1941), who became full professor for paediatrics in 1913. Czerny emphasized in his works the correlation between nutritional disturbance and the behaviour of the child and several diseases were named after him (Czerny-anaemia, Czerny-diathesis, Czerny-respiration).

Tragically, most of the fruitful efforts at the Charité ended unhappily. Kramer left Germany in 1938 and spent the rest of his life in the Netherlands where he was able to find work as a doctor in Amsterdam and Den Dolder. Pollnow emigrated in 1933 to Paris, but as war raged he was caught by German troops in southern France and later murdered in Mauthausen.
Franz Kramer (on the left of the first row), Hans Pollnow (standing in the second row, two from the right) and colleagues of the "Kinder-Kranken- und Beobachtungsstation" at the Charité around 1929.


Kramer and Pollnow

Franz Kramer (1878–1967) and Hans Pollnow (1902–1943) owe their place in the history of child and adolescent psychiatry to their work on the description of hyperkinetic syndromes and conditions that culminated in their landmark article Über eine hyperkinetische Erkrankung im Kindesalter, published in 1932. In this article, Kramer and Pollnow described a case series of 17 children who presented with aggressive behaviour, impulsivity, chaotic motor restlessness and learning difficulties, syndromes consistent with what is now regarded as ADHD or hyperkinetic syndrome. This clinical picture was later named Kramer-Pollnow syndrome.

Medical record written by Franz Kramer. Charité, March 17, 1926.
Part III
Towards medication of "uncontrolled" behaviour
The Emma Pendleton Bradley Home

The Emma Pendleton Bradley Home was America's first neuropsychiatric hospital for children, and named for George and Helen Bradley's only child Emma Pendleton Bradley (1879–1907), who had been stricken with encephalitis as a young child. In his will, the affluent businessman George Bradley (1846–1906), who among other activities had helped Graham Bell to market the telephone, requested that the Baton House, the family’s Providence estate, be converted into a treatment facility for children. The institution opened its doors in 1931 in a new, less urban, setting and in accordance with the terms of George Bradley’s will, the facility gave first preference to poor, needy children from Rhode Island and families were only billed if they had the means to pay.

Owing to its focus on child psychiatry, the Emma Pendleton Bradley Home attracted many talented researchers who made seminal contributions to the investigation of ADHD.
Emma Bradley was stricken with encephalitis at the age of seven. The disease left her with multiple disabilities, including epilepsy, mental retardation and cerebral palsy. This tragedy sparked the Bradleys to conduct a worldwide search for a cure or treatment for Emma’s condition. As psychiatry and neurology were in their infancy, hospitals were solely for adults and pediatric services were not yet available, the Bradleys arranged around-the-clock medical care for Emma at their summer home in Pomfret, Connecticut. After eighteen years of treatment, Emma showed no improvement, and George and Helen began to accept their daughter’s fate.
Psychostimulants

Psychostimulants, drugs employed to elevate mood, are regarded as useful tools in managing a range of disorders, including depression and the akinesia of Parkinson’s disease. Pharmacological agents have been used with this aim for centuries; in the 19th century they were known as “nerve tonics”, and included a number of plant-derived agents, including strychnine and cocaine.

A traditionally, well-known agent to stimulate and to enhance concentration was ephedrine, a salt that was isolated from the plant *Ephedra vulgaris* in 1885 by the Japanese chemist Nagayoshi Nagai. Similar in structure to the synthetic derivatives amphetamine and methamphetamine, ephedrine is still used in kampo, the traditional Chinese herbal medicine practiced in Japan, and is still very popular in China as ma-huang. Nagai later synthesized methamphetamine from ephedrine, and his compatriot Akira Ogata (1887–1978) succeeded in crystallizing it in 1919.

Amphetamine was first synthesized in 1887 by the Romanian chemist Lazar Edeleanu at the Humboldt University in Berlin, but was largely unknown until the Philadelphia-based company Smith, Kline and French introduced an inhaler and bronchodilator in 1932 under the trade name “Benzedrine”. It was freely available through the 1930s, when its stimulant properties were first recognized, leading to its widespread use by troops during the Second World War.

Although it might seem counter-intuitive, psychostimulants have proved to be particularly effective in the management of ADHD and a panel of drugs has been researched and used to treat ADHD, particularly amphetamine and methylphenidate.

While other medications are prescribed to manage symptoms of the disorder as well as co-existing symptoms of mood disorder or anxiety, a non-stimulant substance used to treat ADHD is atomoxetine.

By Paul Foley, Sydney, Australia.
Nagayoshi Nagai (1845–1929) was born in Tokushima, Japan, the son of a doctor, and commenced studying medicine at the Dutch Medical School of Nagasaki in 1864. He continued his studies in Tokyo and Berlin, and studied chemistry in the laboratory of A.W. Hofmann (1819–1892). He lived in Berlin from 1871–1886, and was married to Therese Schumacher who spent the rest of her life with him in Japan.

Nagai isolated ephedrine from the plant *Ephedra vulgaris* in 1885 and recognized it to be the active component of the plant. Later, he synthesized methamphetamine from ephedrine. Nagai was a staunch supporter of scientific and cultural exchange between Germany and Japan, and the first president of the *Pharmaceutical Society of Japan*.

*From Japan*

Nagayoshi Nagai in 1917.

School performance

One year after the opening of the Emma Pendleton Bradley Home, the grandnephew of George Bradley, Charles Bradley (1902–1979), joined the staff and soon became medical director. Bradley treated children with post-pneumoencephalography headaches (supposedly due to spinal fluid loss) with benzedrine that he received from Smith, Kline and French Laboratories in Philadelphia. He presumed that a stimulant drug would stimulate the choroid plexus to produce spinal fluid. While the drug did not do much for the headaches, teachers noted that some of these children performed markedly better at school, obviously due to the benefical effects of benzedrine. Bradley pursued this serendipitous discovery in a controlled trial and reported in his landmark article of 1937 that 14 of 30 children with behaviour problems showed a spectacular change in behaviour and improved school performance during one week of treatment with benzedrine.

Bradley’s observations were important discoveries, and follow-up studies established the benefit of psychostimulants in the treatment of ADHD. Well aware that most of the psychological afflictions of children had no effective treatment, Bradley felt that more people needed to be educated and trained in child psychiatry, and moved in 1948 to the University of Oregon Medical School to found and direct a department of child psychiatry.

“Possibly the most striking change in behaviour during the week of benzedrine therapy occurred in the school activities of many of these patients […] …a great increase of interest in school material was noted immediately. There appeared a definite “drive” to accomplish as much as possible during the school period, and often to spend extra time completing additional work […] The improvement was noted in all school subjects. It appeared promptly the first day benzedrine was given and disappeared on the first day it was discontinued.”

Charles Bradley, 1937, p. 578.
Benzedrine is the trade name of the racemic mixture of amphetamine (dl-amphetamine) and was marketed under this brand name in the United States in the form of inhalers. Benzedrine was used to enlarge nasal and bronchial passages and is closely related to other stimulants, such as Dexedrine (d-amphetamine) and methamphetamine. Benzedrine was initially employed for medical purposes, but early users soon discovered its euphoric stimulant effect, making it one of the earliest synthetic stimulants for recreational purposes and brain doping. In the 1940s and 1950s, reports began to emerge about the abuse of inhalers, and the FDA finally listed it as a restricted drug in the United States.
B
orn in Italy in 1907, Leandro Panizzon grew up in Milan and studied chemistry at the University of Basel. Having completed his dissertation and postdoctoral study in Birmingham, Panizzon was hired by the Swiss pharmaceutical company CIBA, where he was in charge of researching nitrogenous organic compounds, particularly derivatives of pyridine. One of his early successes was the discovery (together with Marx Hartmann) of a diuretic in the 1930s, later marketed under the brand name Esidron. His masterpiece, however, was the synthesis of methylphenidate in 1944. While he was not overly impressed by the results of a self-experiment, the enthusiasm of his wife Marguerite, nicknamed Rita, was greater, and she enjoyed the stimulating effects of the substance before playing tennis. Panizzon thus named the substance Ritaline, also its brand name when CIBA introduced it in Germany and Switzerland in 1954 promoting the drug as a psychotonicum to relieve chronic fatigue and mild depressions.
Part IV
From etiology to understanding and management of ADHD
A family affair

The clustering of ADHD in certain families is a well known phenomenon early described in the scientific literature. It has been discussed with regard to predisposing psychosocial family risk factors, genetic influences as well as gene-environment and gene-gene interactions.

Genes play a significant role as etiological factors of ADHD, and Kramer and Pollnow already mentioned a case of monzygotic twins with the core symptoms of ADHD in their seminal article. Initial family studies were later supplemented by adoption and twin studies showing a heritability that explains on average about 80% of the phenotypic variance in the population (such as papers by the groups of Biederman, Faraone, Thapar and others). Molecular genetic studies indicate the multifocal genetic influence of a remarkable number of different gene loci distributed on different chromosomes. Further genetic investigations reinforce the hypothesis that abnormalities in the neurotransmitter system are a crucial predisposing factor, e.g. that there is an association with multiple transporter genes.

Environmental family risks associated with ADHD include unspecific pre- and perinatal disorders, exposure to alcohol and smoking during pregnancy, and psychosocial adversities such as severe deprivation in early childhood. Studies of family interaction and family life quality indicate a long lasting irritating influence on this behavioural disorder. Morrison and Stewart (1971) were the first authors who presented empirical results with regard to the high prevalence of increased alcohol abuse, antisocial behaviour and hysteria in parents of children with ADHD. Their results were confirmed one year later by Dennis Cantwell in a cohort of similar size. Longitudinal studies which showed that ADHD may persist into adulthood commenced in the late 1960s with the paper by Menkens et al. (1967) and the studies by Mendelson (1971) and Stewart (1973).

ADHD is thus a disorder influenced by a complex interaction of genetic, non-genetic-organic, and environmental etiological factors. There exists a behavioural disposition of the individual, but it is almost always a family issue, too.

"Genetic influences are known to be strong. Nevertheless, naïve reductionism is unlikely to be enough for understanding. What is inherited appears to be a set of traits rather than an illness, and a set of dispositions to react to the environmental associations of ADHD."

Eric Taylor, 2011.
Neurotransmitters

Neurotransmitters are the chemical messengers which convey messages between nerve cells in the brain. A perhaps surprisingly small panel of chemicals have been selected by evolution to execute the complex functions of the central nervous system, with differences in the distribution of different receptor types and the responses they induce inside the cells which carry them, and the different topographical distribution of different nervous pathways which allows the complexity of communication and response which characterizes the human brain. This limited panel of neurotransmitters has both advantages and disadvantages for the development of agents to ameliorate the effects of brain disorders. The major disadvantage is that even if one identifies that a chemical deficit, imbalance or other abnormal condition primarily involves a particular transmitter system, it is difficult to achieve the desired re-adjustment by chemical means without affecting – perhaps in a negative fashion – other aspects of brain function.

The neurotransmitter most commonly implicated in ADHD is dopamine. Once considered nothing more than an intermediate product in the synthesis of the other two catecholamine transmitters, adrenaline and noradrenaline, it is now recognized that dopamine is essentially involved in a variety of functions, including the control and modulation of emotivity and reactivity, concentration, reasoning, and the co-ordination of motor function. An abnormally low level of effective dopamine can cause the three primary symptoms of ADHD: inattention, impulsiveness, and hyperactivity. Mechanisms involved in the metabolism of dopamine may cause this low level: reduced production, increased re-uptake by transporter molecules or catabolism, reduced receptor response to released dopamine. The fact that stimulants increase the levels of dopamine and other neurotransmitters (including epinephrine and serotonin) and help reduce ADHD symptoms suggests that complex interactions between these neurotransmitters underlie ADHD.

A disorder as complex as ADHD is, however, unlikely to be based upon the dysfunction of a single neural system and other transmitters may thus be involved. Noradrenaline has been implicated in animal studies as being involved in inhibitory pathways which reduce impulsive behaviour. Low brain serotonin levels have been associated with aggression and suicidal behaviour in humans. The exact nature of this role remains, however, to be elucidated; one of the major problems for investigators is the existence of at least 14 serotonin receptor subtypes, some of which are modulated by catecholamine transmitters. There are currently no ADHD medications which target serotonergic transmission. Impaired glutamatergic transmission in the prefrontal cortex has been linked with increased impulsivity in animal studies, but has not yet been investigated in humans.

By Paul Foley, Sydney, Australia.

Developmental comorbidity

In the majority of individuals affected by ADHD, co-existing problems as well as psychiatric and non-psychiatric comorbid disorders occur (Gillberg et al. 2004, Biederman et al. 2006). Co-morbidity often results in serious functional and psychosocial problems in everyday life.

The expression “co-morbidity” in clinical epidemiological research was coined in the 1970s by Alvan Feinstein to denote “any additional co-existing ailment” in addition to index disease (Feinstein 1970). In the context of psychiatric literature, the term “comorbidity” was applied for the first time in the mid 1980s (e.g. Barlow et al. 1986, McGlashan 1987, Sanderson et al. 1990). Biederman and colleagues reviewed the topic of ADHD and associated disorders in 1991, using the term “comorbidity” (Biederman et al. 1991). Aims of research on comorbidity were to define more homogeneous subgroups of patients and to contribute to an aetiology-based classification system. Different theoretical models evolved to explain possible causal links between ADHD and comorbid conditions (e.g. Rhee et al. 2008).

“Developmental comorbidity” describes the concept of the age- and development-dependent occurrence of comorbid disorders, thereby differentiating between distinct trajectories of symptom course (Taurines et al. 2010). Concerning temporal order of manifestation, comorbid conditions may appear before the identification of definite ADHD symptoms - as “pre-comorbidity”. In this context, temperament factors, sleep disturbance, autism spectrum disorders and atopic eczema have been described.

Comorbidity may coincide with the emergence of clinically significant ADHD symptoms, as “simultaneous comorbidity” (e.g. developmental dyslexia, enuresis, encopresis). However, most comorbid disorders are manifested after the onset of ADHD in the course of disease, including anxiety disorders, tic disorder, depression and suicidality, obsessive compulsive disorder, conduct and substance use disorders, bipolar disorder, obesity and personality disorders (“post-comorbidity”). A typical example of distinct symptom progression is the initial appearance of ADHD symptoms, followed by symptoms of oppositional defiant disorder, conduct disorder and, finally, depression (Ostrander et al. 2006, Loeber et al. 2009). Another possible trajectory is the sequence of ADHD, tic disorder and obsessive compulsive disorder (Freeman et al. 2007). However, somatic comorbidity also has to be mentioned in this context; in some patients, early atopic eczema precedes ADHD symptoms, with a modulatory role for sleep disruption (Schmitt et al. 2013). As distinct trajectories of symptom progression and comorbidity impact on therapy, long-term outcome and prognosis of ADHD (e.g. Connor et al. 2010), not only the manifestation of ADHD core symptoms, but also of developmental comorbidity should be accounted for in the diagnostic and therapeutic process.

By Regina Taurines, Würzburg, Germany.

Baseline characteristics regarding comorbidity ADHD in the MTA Cooperative Group Study of 1999 (n=579).

- Baseline characteristics regarding comorbidity in ADHD.
- Data according to the MTA Cooperative Group Study, 1999 (n=579).
Due to its sensitivity to brain metabolism, local or generalized blood flow, brain lesions and chemical agents, electroencephalography (EEG) has been used to analyse behaviour disorders throughout the 20th century. One of the first relevant contributions was a study by the EEG pioneer Herbert H. Jasper (together with Philip Solomon and Charles Bradley) in 1938 that showed distinctly abnormal electroencephalograms in the majority of a group of 71 behaviour problem children from the Emma Pendleton Bradley Home. Further EEG studies (e.g. evoked potentials, brain mapping) also shed light on the effects of psycho-stimulants and revealed that the EEG of ADHD patients is characterized by increased slow and decreased fast activity (Barry et al. 2003).

Along with such new insights, the 1980s saw the deployment of other imaging techniques. Important observations came from Hans Lou and his group, who studied three-dimensional regional cerebral blood flow (rCBF) in children with dysphasia and/or attention deficit disorder by applying Xenon 133 inhalation, a technique pioneered in Scandinavia in the 1960s. In all eleven patients with attention deficits in the 1984 study, Lou found hypoperfusion in the white matter of the frontal lobes, and also hyperperfusion in the caudate region in seven. In a similar study in 1989, Lou and colleagues refined their selection of patients and confirmed their previous results. Additionally, they observed that striatal dysfunctions can be partly reversed with methylphenidate, evidence that low striatal activity is involved in ADHD.

Another interesting contribution was a study by Zametkin et al. in 1990. Using positron emission tomography (PET), pioneered in the 1960s by David Kuhl and Roy Edwards, the authors measured cerebral glucose metabolism in a group of 25 hyperactive adults and 50 control subjects and found a significant decrease of metabolic activity in frontal and striatal regions.

Also at the beginning of the 1990s, researchers deployed magnetic resonance imaging (MRI), together with its related procedure functional MRI (fMRI) a widely used technique based on the work of Raymond Damadian, Paul Lauterbur and Peter Mansfield in the 1970s. The first studies were performed by Hynd and colleagues and aimed to observe deviations in patterns of brain asymmetry.

Since these initial efforts, various studies have produced seminal results for the understanding of ADHD by suggesting that frontostriatal dysfunction is central to pathophysiology, that abnormalities of frontostriatal circuits, modulated by dopamine, exist, that structural abnormalities observed in children in frontal, striatal, parietal and cerebellar regions may be due to a delay in structural brain maturation and that widespread neural deficits in multiple interconnected systems of the brain are present. More research, however, is necessary to find out if non-frontostriatal regions are affected, too, what their contribution to the disorder may be and if brain stimulation techniques may serve as additional non-pharmacological treatment options for ADHD patients.

Images of the brain
Are drugs enough?

**SCIENTIFIC ARTICLES**

**Diagnosis and Treatment of the Hyperactive Child**

STELLA CHESS, M.D., NEW YORK CITY

(From the Department of Psychiatry, New York Medical College, Flower and Fifth Avenue Hospital, and the Mental Hygiene-Child Guidance Clinic, Metropolitan Hospital)

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"Treatment of the hyperactive child utilizes [...] guidance of parents, direct psychotherapy, medication, and auxiliary techniques such as remedial reading and tutoring."

Stella Chess, 1960, p. 2382.

"In 22 cases, or in more than 60 per cent of the physiologically hyperactive children in the study, it was possible to work successfully with the parents on a consultative basis without direct work with the children and without the use of drugs."

Stella Chess, 1960, p. 2383.

"The use of pharmacological agents, such as amphetamine sulfate, offers a supplementary and relatively untried approach to the treatment of children’s psychiatric problems. This approach is no sense replaces that of modifying a child’s surroundings and so removing the sources of conflict. Neither can it offer the same assurance of mental health as do forms of psychotherapy which enable a child to work out his emotional problems, or which train him to deal with future difficulties. However, distressing surroundings cannot always be altered, and lack of facilities frequently make effective psychotherapy impossible. In such situations the simple administration of a drug that produces an improved social adjustment or accelerated school progress may offer considerable assistance to some children."

Bradley and Bowen (1941) on the use of pharmacological agents.

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Given its sedative effects, potassium bromide was among the first medications used to alleviate the burden of ADHD-like symptoms. With the seminal experiments of Charles Bradley, amphetamine sulfates were introduced as treatment options, as were later more refined psychostimulants. Additionally, several other agents have been tested in adult studies, among them bupropion, clonidine, guanfacine, modafinil, pargyline, MAO-B-inhibitors and l-deprenyl (selegiline).

As controversy remains about the use of psychostimulants in children, other valid treatment options include therapies and measures directed to improve behaviour, social skills and environmental aspects. Such comprehensive approaches have been advocated throughout the history of therapeutic options and ultimately gained ground with the works of Stella Chess in the 1960s and of Virginia Douglas (“Are drugs enough?”) in the 1970s. Further support came from Susan Campell, a colleague of Douglas at Montreal’s McGill University, and interesting contributions regarding classroom environment were provided by Teodoro Ayllon and his group.

Their suggestions included parent counselling and guidance, special requirements for educational staff and classroom management, cognitive training programs for children to improve cognitive tasks, social performance and disruptive behaviour, and psychotherapy. They stressed self-evaluation and self-control of affected children, and looked to behavioural alternatives to control hyperactivity, an approach more valid than ever for those interested in long term solutions for treating children with ADHD.
A lifespan issue

When Time magazine headlined on July 18, 1994, that “not just kids” suffered from ADHD, there was already strong agreement that ADHD affects adults as well as children. The hypothesis of a lifespan disorder was tested in various studies from the late 1960s on, when Miriam Menkes and her group presented data of a 25-year follow up study on hyperkinetic children. Of 18 fully re-examined patients, “hyperactivity was still present in three subjects aged 22 to 23 years and had disappeared between the ages of 8 and 21 in the others.” Further longitudinal studies in the following two decades (e.g. Mendelson and colleagues; Weiss and colleagues; Gittelmann and colleagues) showed that symptoms indeed persisted into adulthood, a diagnosis also supported by studies on the efficacy of psychostimulants in adults (Wood and colleagues 1976 and studies by Paul Wender).

As one of today’s burgeoning areas of inquiry, research on ADHD in adults will surely have its place in the upcoming decades along with research on neuroanatomy, comorbidity, genetics and therapy. While the chances of full regression of ADHD symptoms during early adulthood are not great, an interesting social aspect seems to be life quality of all affected age groups as well as only indirectly affected healthy parents. As recent longitudinal comparisons between patients with simple disorders of activity and attention and patients with a hyperkinetic conduct disorder by Remschmidt and Mattejat (2010) have shown, the latter group underperformed in life quality improvements, and their parents suffered more.

It may thus be a worthwhile future endeavor to focus greater attention on life quality issues, on the effect of ADHD on daily life and work environment, and to transfer knowledge to geographic areas where social awareness is not yet as high as in countries with a strong historical background in ADHD research.

“Environmental contributions have been rather under-researched and under-emphasised until recently, and I would argue that social and cultural influences have yet to be given their full importance. There are probably strong cultural influences, not on the neurobiological variation, but on the extent to which it leads to impairment or to disability – and especially to diagnosis. The differences between cultures in recognition and acceptance are not just trivial nuisances in ascertaining a “true” prevalence rate. They emphasise that the extent of impairment is a function not only of the children but of the context in which they are growing up. I suggest that public and professional attitudes can be helped by learning from history the interplay between scientific understanding and social change.”

Eric Taylor, 2011.
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