If we take in our hand any volume...let us ask, Does it contain any abstract reasoning concerning quantity or number? No. Does it contain any experimental reasoning, concerning matter of fact and existence? No. Commit it then to flames: for it can contain nothing but sophistry and illusion.

David Hume [1]

Introduction

Historians recognize that there are many different forms of historical investigation [2]. However, Hume’s dictum reminds us that a truly scientific history of ADHD has yet to be written; that is, a quantitative account of how various antecedent variables contributed to ADHD as a dependent variable. Consider, for example, the number of peer-reviewed papers using the keywords, “Attention Deficit Hyperactivity Disorder” (Figure 1.1).

The exponential growth in scientific papers shows an approximate doubling in number of references with each half-decade. This beautiful law-like curve calls out for an explanation in quantitative terms. An exact scientist would be inclined to ask, to what extents do various scientific discoveries; modes of thinking; social, political, economic, or other forces act as causes for the remarkable rise in awareness of the concept of ADHD? Some weighted combination of variables might then resolve the persisting controversies of what caused the upsurge of interest in ADHD and how much each component variable contributed to the outcome. However, until such a history is written it will be necessary to opt for Aristotle’s advice that, “If you would understand anything, observe its beginning and its development.”

There are already several competing views of the history of ADHD. Regarding the basic symptoms of ADHD, one such recent account by Rafalovich assumes that, “The history of compiling these symptoms into formal diagnoses represents an increasing drive to medicalize unconventional childhood behavior.” [3, p. 94]. He rejects both the “child control” explanations for ADHD by Schrag and Divoky [4] and Peter Breggin [5]; as well as Barkley’s [6–8] and Kessler’s [9] characterization of ADHD as the slow progress towards scientific validity. He finds those different approaches both too brief and “disturbingly ideological” ways of serving their own agendas. Another recent account sees ADHD’s hold on scientific interest as the product of a down-and-out struggle between psychoanalysis, social psychiatry, and modern neurosciences, in which the neurological basis of the disorder was a recent outcome of the winner of the struggle [10].

Figure 1.1. The number of citations of ADHD in titles of Ovid Medline citations database. “Attention Deficit Hyperactivity Disorder” was used as a search term for all English and foreign language citations for each 5-year period between 1970 and 2009.
While there are undoubtedly some truths buried in each of those accounts, I will argue that the neurological and scientific basis of ADHD began in the early eighteenth and nineteenth centuries with a particular model of mental illness, the idea that overstimulation causes disinhibited and immoral behavior due to a neurological weakness. This idea was later followed by a paradigm shift in taxonomic thinking about diagnosis which revolutionized how the illness was defined, allowing a union of the older ideas of inattention and overstimulation with recent developments in neuropsychology and neurosciences.

Our history of ADHD will focus on the various factors leading to and enhancing the growth of the scientific awareness of ADHD in our time, though one cannot ignore the non-scientific outcries against it, since in its own way vocal resistance to the concept also contributes to the notoriety, if not true understanding, of the concept.

**Pre-scientific origins of ADHD: Zeitgeist and famous men**

I believe that the idea of ADHD did not begin with the commonly mentioned pioneers given credit for initiating the “medicalization” of the concept, but rather with a deep-seated model of mental illness which dominated eighteenth- and nineteenth-century thinking, and which to a large extent still pervades our own culture. This period formed the zeitgeist or background for a particular paradigm of scientific understanding.

“The inscrutable Zeitgeist” was Goethe’s term that he used in 1827 for “the source of events that occur neither by agreement nor by fiat, but self-determined under the multiplicity of climates of opinion,” (quoted from Edwin Boring’s classic paper on the Zeitgeist and Psychology of Science, in which he contrasts the Zeitgeist with the “Great Man Theory” of scientific progress) [11, p. 13]. The history of ADHD has *both* famous men and a Zeitgeist, which partially accounts for the steady progress towards today’s conception of ADHD. As it usually turns out, the “famous man” chosen by history as the innovator of a turning point merely represents the confluence of ideas already widely current in his or her time.

Palmer and Finger called attention to one such famous man [12], a very early neglected figure who succinctly described in 1798 what is now known as the Inattentive Subtype of ADHD. Sir Alexander Crichton was a Scottish physician widely known in his time for his treatise on mental illness [13]. With amazing prescience he stated:

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. 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. In this disease of attention, if it can with propriety be called so, every impression seems to agitate the person, and gives him or her an unnatural degree of mental restlessness. People walking up and down the room, a slight noise, the same, the moving of a table, the shutting a door suddenly, a slight excess of heat or cold, too much light or too little light, all destroy constant attention in such patients, inasmuch as it is easily excited by every impression. [p. 272]

Note how Crichton refers to patients with this “disease” – one he obviously was familiar with from his own practice. He was aware that the condition existed in various degrees in otherwise normal individuals, had a deleterious impact on educational attainment, and that it often diminished in severity with age. The “morbid sensibility of the nerves” squarely points to a neurological basis of the disorder.

Crichton’s work was in general accord with the thinking of the time, as may be seen in another widely read and respected work of the nineteenth century on mental illness, George Mann Burrows’ 1828 *Commentaries on the Causes, Forms, Symptoms and Treatment, Moral and Medical, of Insanity* [14]. He published his commentaries just 30 years after Crichton’s treatise, based upon his own clinical experience and a scholarly review of world literature. He was probably well aware of Crichton’s treatise in the tightly knit British Royal Society.

The moderns divide the cause of insanity into moral and physical. Every impression on the sensorium, through the external senses, and every passion in excess, may become a moral cause of insanity. Thus all, however opposite, act as exciting causes, and will produce this result: joy and grief, anger and pain, love and hatred, courage and fear, temperance and ebriety, relotion and ination, application and indolence may have the same effect. Vices, also, which occasion
changes in the physical constitution, act as remote moral causes, and induce mental derangement. [p. 9]

What today appears as a quaint preoccupation with “moral” causes was in fact a specific theory in which moral behavior depended upon the regulation of stimulation to the brain. Too much stimulation acted to divert action away from correct choices towards immoral, unlawful, or antisocial behavior. Attention and its opposite state of distraction were the keys for selecting the correct or “moral” choice.

This theme of the centrality of attention in behavior was reinforced in 1890 by William James (Figure 1.2) [15], the most widely known scholarly psychologist of the day.

Every one knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalizations, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatter-brained state which in French is called distraction. [p. 403]

Thus, a coherent picture emerged in the nineteenth century in which overstimulation of any kind could produce a picture of misbehavior, due to some fundamental weakness in the nervous system. This idea was widely known in both academic medicine and psychology, as well as among the general public.

The awareness of physicians and the lay public of the impulsive, disruptive behavior pattern was particularly influenced by a German psychiatrist, Heinrich Hoffman (Figure 1.3), whose doggerel verse and charming picture book appeared in 1845, and became very popular throughout Europe. Influences from Hoffman’s observations continue even to the current day in art, music, and literature; for example in the movie of Edward Scissorhands, stage plays, commemorative stamps, and new editions in English [16]. Hoffman’s book portrays several troublesome children, each teaching a particular moral lesson. “Fidgety Phil,” or “Slovenly Peter” as Mark Twain called him from his own translation into English, is an impulsive, naughty
extensive commentary linking many of Still’s observations to current interpretations of causes for ADHD.

In keeping with the beliefs of his time, Still argued that the children he studied suffered from a “moral” defect, which meant that their behavior, which was “against the good of all,” arose from a defect in focusing of conscious attention towards correct behavioral choices. He alludes to William James’ theory of attention as the basis for that force of will, which is required for channeling one’s behavior along acceptable societal and educational paths. He included in his list of behavioral characteristics a “passionate” or highly emotional state, lawlessness, spitefulness, cruelty, and dishonesty. (Some might argue that Still should be considered the father of Conduct Disorder, or Oppositional Defiant Disorder, rather than ADHD.) But undeniably he put his finger on some key features of ADHD such as a failure of volitional control or inhibition, and excitable or impulsive behavior in otherwise normal children.

Rafalovich, a historian of sociology of medicine, argues that the nineteenth century’s accepted wisdom regarding the nature of mental illness, rather than Still’s lectures, was the driving force that is the true progenitor for the ADHD concept [3]. He gives Still credit for realizing that there was a continuum of intelligence extending from the imbecile to normal children, and that there was a deviant behavior pattern that could be observed in the otherwise normal children:

It is more germane to study medical concepts that were en vogue at the time of Still’s research: idiocy, and, more significant for Still, imbecility… I argue that Still was the first to link the notion of imbecility to the morality of children, even though he failed to provide an official diagnosis for this childhood behavior. [p. 98]

Rafalovich points out that the idea of moral insanity (“moral imbecility”) involving reckless and shameful behavior in children antedated Still’s report by several years [p. 102]. His historical analysis treats Still’s work as a plea to the medical community rather than a critical medical discovery, with modern accounts by Barkley and Kessler also simply dismissed as a misrepresentation “which distorts the experimental and conceptual history that has given us the legacy of ADHD.” [p. 104]. This comment should be seen as an example in which the Great Man Theory of history is less preferred than The Zeitgeist as an explanatory model for scientific progress. It is in line with the historian Bor ing, who says what matters is not any particular man,
but “the total body of knowledge and opinion available at any time to a person living within a given culture” [11, p. 13].

Rafalovich also argues for the importance of the behavioral picture resulting from the pandemic of *Encephalitis Lethargica* as more relevant to the origins of ADHD than Still’s lectures. There can be no argument about the relevance of that great pandemic to the line of investigation which ultimately led to the discovery of the role of stimulant drugs, and the subsequent upsurge of research on ADHD. Regardless of which position one takes on the issue of Still’s priority in the development of the ADHD concept, there is little doubt that events shortly after his presentation had a major impact on the history of ADHD. Sixteen years after Still’s lectures a pandemic of influenza caused a disastrous episode of *Encephalitis Lethargica* or sleeping sickness, known as *von Economo’s encephalitis* [19], in which 20 million people worldwide were estimated to have died from the illness. The disease was complex, with many sequelae and an uncertain course, often re-occurring after long periods of apparent recovery.

A key feature of *Encephalitis Lethargica* was the contrast of the normal personality preceding the illness with the subsequent deranged behavior [20]. However, the disease was complicated by as many as 27 different symptoms [9] and apart from the obvious motor signs, there were personality features that mimicked the cunning antisocial behavior and moral lapses of children without the disease [21]. Because of the complexity of the disease and cases with a long interval between onset and re-occurrence of symptoms, there were bound to be cases of behavior disorder that could be attributed to an unknown earlier episode of encephalitis. Therefore the classic logical error of *post-hoc, ergo propter hoc* (“after this, therefore because of this”) was sometimes made. Thus began a period of uncertainty when it was not always clear whether a behavior problem in a child was due to “brain damage” or some other “functional” cause.

**Encephalitis and early psychopharmacology**

Pasteur’s “fortune favors a prepared mind,” was never more apt than in Charles Bradley’s serendipitous discovery of the role played by stimulants in the treatment of behavior disordered children. Bradley’s great uncle, George Bradley, had a daughter severely impaired by *Encephalitis Lethargica*, which caused him to found a hospital in Providence, Rhode Island for her care, subsequently known as the Emma Pendleton Bradley Hospital for Children. George Bradley appointed his great nephew Charles as the first medical director of the hospital. Charles Bradley was a psychiatrist fresh out of his residency at New York’s famous Bellevue Hospital, where he developed a strong belief in the biological origins of mental illness (Figure 1.5).

In his new role at the Bradley Hospital, Charles was confronted with the common problem of distinguishing the post-encephalitic behavior disorders from those without a known history of infection or brain injury. Using the only available brain imaging technique of the day, he routinely collected pneumoencephalograms (sometimes known as PEG) on the new cases. This technique requires draining cerebrospinal fluid and replacing it with air in order to allow the structure of the brain to show up more clearly on X-ray. It was introduced in 1919 by the neurosurgeon Walter Dandy at the height of the pandemic of *von Economo’s encephalitis*. Fortunately Bradley had received training in this technique during his residency. Now totally abandoned due to the superior imaging technologies of MRI and CT scans, PEG typically produced severe, painful headaches.

Bradley reasoned that if he could stimulate the choroid plexus surrounding the ventricles he
could alleviate the headaches. To accomplish this he treated 43 of the children with Benzedrine, the trade name of the racemic mixture of amphetamine (d,l-amphetamine). Bradley was promptly informed by his teachers and staff that about half of the children had suddenly become more calm, organized, and effective in their learning. The children came to view the pills as “math pills” because of their apparent effect in allowing them to do sums that heretofore had been difficult or impossible because of their unfocused and restless behavior. Bradley noted that although the children became subdued, they also remained alert and focused [22]. The results prompted him to continue the treatment and he later published a series of 100 children between ages 5 and 12 years, including 77 boys and 23 girls [23].

Bradley’s ultimate influence on the progress towards ADHD went far beyond this introduction of stimulant treatment, for he established a tradition of close observation and experiment at the Bradley Hospital which continued well after he departed. Maurice Laufer, a child psychiatrist, was to become the new medical director of the Bradley Hospital (Figure 1.6).

Laufer and his child neurologist colleague, Eric Denhoff, began a series of experiments and clinical studies on children they described as having Hyperkinetic Impulse Disorder. What was unique was the creation of a set of formal criteria for selecting the patients for their studies [24–26]. These included:

- Hyperactivity
- Short attention span
- Poor concentration
- Variability in performance
- Impulsiveness
- Inability to delay gratification
- Irritability and explosiveness
- Poor school work.

These criteria anticipated by more than three decades a very similar symptom list in the new Diagnostic and Statistical Manual (DSM) in its various revisions. Laufer and colleagues thought of hyperkinesis as the “cardinal” symptom for their new appellation of a Hyperkinetic Impulse Disorder.

Laufer and Denhoff were careful to point out that many of these hyperkinetic children were anxious, but not in the sense of neurotic anxiety often seen in the clinic; but rather as a result of their difficulties at school and in relationships with peers. They also were careful to note the difference between poor school work as a part of the syndrome, and more specific learning disorders. Perhaps regretfully, the DSM committee later removed poor school work from their list, as well as the criteria of variability and irritability/explosiveness. (The latter is likely to be reinstated, controversially, in the form of temper dysregulation disorder in DSM-5.)

Also unique in their day was the hypothesis that defective filtering of external stimuli by the diencephalon was responsible for the behavior of the hyperkinetic impulse disorder. Thus, the venerable notion that pervaded nineteenth-century thinking, *excess stimuli flooding the brain* and causing the behavioral and attentional syndrome, reappeared with Bradley and his successors at the Bradley Hospital. They based this idea on their findings from a daring (and now impossibly controversial) experiment, measuring the threshold of photo-stimulation activation of metrazol-induced seizure patterns on the EEG. They reported that this threshold was lower for children with the hyperkinetic impulse disorder. This experiment has never been repeated, and presumably never will, given the risk/reward problem in such an experiment.

There is little doubt that the striking clinical effect of the stimulant drugs, which began with Bradley and
his colleagues, propelled a movement towards a true period of psychopharmacology with children, as well as the search for a more satisfactory diagnostic framework. The next several decades would see a flourishing of efforts to characterize a specific syndrome or diagnostic entity that is both reliable and valid, and which would eventually allow a true scientific union with genetics, neuroscience, and therapeutic trials.

**Minimal brain dysfunction**

In 1908, soon after Still's lectures, it was hypothesized by Tredgold that children with disruptive, hyperactive behavior without demonstrable brain damage may have suffered mild injuries during birth, or minimal brain damage [27]. The term “organic drivenness,” also soon entered the literature, referring to a characteristic behavior pattern in children without verified brain damage or illness [28].

Influential educators then began recognizing the importance of special methods of education for such children [29], coming explicitly to the conclusion that “we are justified in diagnosing on the basis of functional rather than neurological signs.” [30, p. 42]. The influential developmental psychologists Gesell and Amatruda (1941), who had enormous impact on child-rearing ideas, stated that “an entirely negative birth history and an uneventful neonatal period may nevertheless demand a diagnosis of minimal injury because of persistent or gradually diminishing behavior signs [31, p. 231]. Thus, it came to be common practice to accept the behavior pattern alone as evidence of brain damage. Between the 1950s and 1970s there was a growing awareness among pediatricians and public health researchers of the impact of early birth and perinatal problems on later development and behavior [31–35]. The notion of a “continuum of reproductive casualty” gave a more substantive meaning to the idea of a behavior syndrome with brain involvement of a possible subtle or minimal level of damage.

In this atmosphere, Sam Clements and John Peters (Figure 1.7), first coined the term *Minimal Brain Dysfunction* (MBD) [36].

Clements and Peters were part of a remarkable group of physicians, psychologists, and educators at the University of Arkansas, which also included Roscoe Dykman and Peggy Ackerman. This team was responsible for many early clinical and laboratory studies on MBD as well as innovative assessment and educational interventions with learning-disabled and educationally handicapped children. Their early suggestion that *specific learning disability*, along with its associated behavioral characteristics, constituted an *attentional deficit syndrome* had a significant impact on subsequent nomenclature. Although others are often given credit for the re-introduction of attention into the diagnostic discourse of ADHD (such as the classic paper by Virginia Douglas called *Stop, look, and listen*) [37], the Arkansas group was actually the first to provide this insight [38]. In a later 1993 discussion of this point, Dykman and Ackerman point out:
This was the first paper to suggest specifically that MBD be replaced by the label attention deficit syndrome. Many people reading the 1971 paper believed that we were talking only about LD [Learning Disability] children, but in fact most of our studies at that time included children who were hyperactive alone [but typically underachieving in one area or another], LD alone, or both. Our belief was that the majority of children referred to our clinic for academic problems were both hyperactive and LD…Our research is very consistent in supporting the idea that attention problems are common to the majority of LD as well as ADD [Attention Deficit Disorder] children. [39, p. 14]

Peters et al. also developed a special neurological examination, a battery of psychological tests, and clear descriptions of the clinical assessment procedures for MBD [40]. Their Physician’s Handbook [41] was an influential teaching guide for recognizing MBD, which brought the condition to the awareness of a generation of medical students, pediatricians, and psychiatrists.

Neurologists resisted the growing trend of attributing the behavior pattern to brain damage. Shortly after the 1963 Clements and Peters paper appeared, the Oxford International Study Group on Child Neurology decided to adopt Clements’ and Peters’ term for the behavior pattern as Minimal Brain Dysfunction or MBD. They elected to retain the notion of brain damage only for those cases in which a known disease preceded the pattern and in which classic focal neurological signs could be detected [42].

Responding to a growing need for a consensus on the features of MBD, a Public Health Service committee headed by Clements in 1966 arrived at an official statement:

This term as a diagnostic and descriptive category refers to children of near average, average or above average intellectual capacity with certain learning and/or behavioral disabilities ranging from mild to severe, which are associated with deviations of function of the central nervous system. These deviations may manifest themselves by various combinations of impairment in perception, conceptualization, language, memory and control of attention, impulse or motor function [emphasis ours]. These aberrations may arise from genetic variations, biochemical irregularities, perinatal brain insults, or other illnesses or injuries sustained during the years critical for the development of the central nervous system [43]. (Interestingly, the last set of symptoms in this list, “control of attention, impulse or motor function,” was the primary concept retained in later formulations of ADHD by DSM-III and DSM-IV. The much broader concept of MBD was winnowed down to subtypes of Hyperactivity/Impulsivity, Inattention, and their combination.)

Wender’s 1971 monograph on MBD further elaborated the clinical description and proposed a central mechanism to account for the clinical picture [44]. In this monograph and subsequent articles [45] he advanced the hypothesis that the disorder was genetic in origin, mediated by decreased activity in dopaminergic systems in the brain. This suggestion of a dopaminergic mechanism preceded confirmation of the hypothesis by several decades, when it became possible to image dopamine synaptic markers with positron emission tomography in ADHD adults [46].

Despite a wealth of historical, epidemiological, clinical, and laboratory studies employing the MBD diagnostic concept, it gradually lost favor for a number of reasons. Critics of the concept of a single syndrome, which includes hyperkinesis, learning disabilities, inattention, and minor motor signs, cited several problems. First, there appeared to be no single or “cardinal” symptom that invariably appeared with the syndrome. Even though Donald and Rachel Klein pointed out in 1974 that a syndrome need not be monothetic, but could instead be characterized by a list of several symptoms from which some minimal number always appeared (i.e., a polythetic taxonomic structure) [47], the long list of qualifying symptoms for MBD inevitably led to study samples of widely differing characteristics.

Second, the role of the brain was always inferential; there were at this period very few direct measures of brain structure or integrity specific enough to warrant consideration. As a result, the diagnosis was often circular, the only evidence for the role of the brain being the behavioral symptoms alone. This is tantamount to the joke about the parent who asks why their child cannot read, and is told that they have dyslexia; and then when asked what causes dyslexia, is told, “Inability to read.”

Third, much of the behavioral evidence showed that hyperactive or disruptive behavior was situational. For example, that the disturbances might be evident only at school, not at home, or vice versa, resulting in a low correlation between measures taken from teachers and parents. The lack of a criterion of
pervasiveness waited for a remedy in the later concept of ADHD.

Fourth, there was an obvious overlap of the proposed symptoms of MBD with other psychiatric disorders. This fatal flaw of the MBD concept was stated by Rutter:

…the nosological status of the hyperkinetic or attentional deficit syndrome remains quite uncertain and lacking in empirical validation. Much of the difficulty stems from the very pervasiveness of the phenomena. Both epidemiological…and clinical studies…have shown that a high proportion of children with psychiatric disorders of all kinds tend to be restless, fidgety, overactive, inattentive, and lacking in concentration…The available evidence suggests that, in and of themselves, the mere presence of overactivity or poor concentration is of no diagnostic importance. Both symptoms may have many quite different causes. Thus, for example, it is well recognized that high levels of anxiety may lead to restlessness and that depression tends to be accompanied by deficits in concentration. [48, p. 581]

Perhaps the strongest empirical indictment of the MBD concept came from the results of the massive perinatal project of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [49]. This project followed over 30 000 children whose mothers were examined from the antenatal period, and whose children were examined from birth to 7 years of age. Symptoms were examined in four major categories: behavior, cognitive/perceptual-motor, academic, and neurological. Factor analyses reduced the number of variables to hyperkinetic-impulsive behavior, learning difficulties, and neurological “soft signs.” (A fourth category of social immaturity was to be analyzed later.) No single “MBD factor” was identified, but the three main groups of “MBD” symptoms became the dependent measures for the predictive analyses.

From the pre- and postnatal periods, 331 variables were screened as possible predictors of symptoms of MBD. These included family history, socioeconomic data, maternal characteristics, pregnancy, labor, delivery, speech/language, and hearing tests. Only about 5% of the three main groups were considered suspicious. These were then contrasted with the completely “normal” remainder of the sample, consisting of 12 511 children. Discriminant function analyses searched for independent contributions to the variance.

The only consistent finding across the three symptom groups was maternal smoking and poor prenatal care. Learning difficulties were more related to demographic variables such as large family size, low socioeconomic status, and frequent changes in residence, than to pregnancy, labor, and delivery factors. The family factors appeared to be associated with demographic rather than genetic variables. (The hyperactive–impulsive factor measures at age 4, however, were consistently related to various impairments in learning and behavior at 7 years of age.) But there were few overlaps between this factor and the neurological indices, suggesting that the “brain” part of MBD had little support from the neurological examination.

**Paradigm shift: the diagnosis of ADHD**

The historian Thomas Kuhn referred to a scientific paradigm as the set of practices that define a scientific discipline at any particular period of time [50]. He included in its meaning what is to be observed and scrutinized, the kind of questions to be asked, how these questions are to be structured, and how the results of scientific investigations should be interpreted. By all of these criteria, the diagnosis of ADHD, beginning with the DSM-III, 1980, stands as a revolutionary paradigm shift [51, 52]. The major feature of this shift was a change from an etiological model to a descriptive behavioral model of mental illness. DSM-I had designated the hyperkinetic behavior syndrome as a reaction disorder in childhood, in keeping with the current psychiatric thinking attributing the behavior to parental and family environment and neurotic conflict. Although the term “reaction” was dropped in the 1968 version, DSM-II, neurosis was still included.

Robert Spitzer, the chair of the DSM-III committee, championed a “neo-Kraepelinian” model of descriptive categories, modified to be similar to the Washington University (“Feighner”) and Research Diagnostic Criteria developed by workgroups at the Washington University of St. Louis and New York State Psychiatric Institute, respectively. These concepts included criteria regarding the age and course of the illness, response to treatment, associated features, and level of impairment.

There is little doubt that the science of ADHD was markedly enhanced by the shift from an etiological approach embodied in both the nineteenth-century Zeitgeist and in the MBD concept. Laufer and
Denhoff’s listing of the criteria for the hyperactive–impulsive behavior disorder, and the Clements and Peters list of symptoms for MBD were important transitional influences because they laid out specific symptomatic criteria, but were framed within the classical medical tradition of an etiological model of disease processes. The rather simple hypothesis of a single brain mechanism in the diencephalon, itself a carryover from nineteenth-century ideas of over-stimulation as the source of mental disease, could now be abandoned in favor of a more refined exploration of the many directly measured brain mechanisms involved in ADHD.

However, despite many criticisms of the MBD concept, researchers looking for a brain-based cause of MBD, once new brain imaging tools became available, would eventually return to neurological explanations. This caused Judith Rapaport and Xavier Castellanos to remark:

> Since the publication of DSM-3-R in 1987…a number of anatomical MRI studies…have in fact documented minimal but significant brain anatomical deviations – ironically, minimal brain dysfunction now takes on new meaning! [53, p. 267]

But the explosive growth of the neurosciences in ADHD was only possible by virtue of stricter behavioral guidelines for selecting cases within a new diagnostic framework.

**Therapeutics of ADHD:**

**Pharmacotherapy and behavior therapy**

The new era of pharmacotherapy, initiated by Bradley’s serendipitous discovery of the impact of stimulants, along with application of the new diagnostic framework using controlled clinical trials, led to a significant burst in the use of stimulants with ADHD. Meta-analyses of stimulant use over a period of several decades showed a consistent enhancement of behavioral improvement with effect sizes ranging from 0.6 to 0.8 [54, 55]. A recent meta-analysis showed mean effect sizes of 0.77 and 1.03 for methylphenidate and amphetamine, respectively [56]. Significant, but lesser effect sizes occurred for academic as opposed to behavioral targets.

Much had been written during the period of MBD attesting to the importance of behavioral methods of treatment, particularly relating to educational intervention, in mitigating the impact of the MBD syndrome on both academic and behavioral functioning. Safer and Allan gave perhaps the earliest and most comprehensive coverage of the concept of multimodal therapy. As Eisenberg stated in the foreword to their 1976 book,

> There is enough evidence now to support the authors’ conclusion that a combined “multimodal” coordinated plan of management makes the most sense. Either-or formulations do violence to clinical reality. A significant feature of this book is its skillful synthesis of multiple approaches into a comprehensive plan of care for children very much in need of our help. It is clear to me that the book is a major contribution. [57]

Almost two decades later hundreds of studies attested to the validity of this prescient statement. In 1992 in response to overwhelming evidence that each treatment individually was effective, the National Institute of Mental Health (NIMH) and the US Department of Education sponsored the largest controlled trial of multimodal treatment of ADHD, known as the Multimodal Treatment of ADHD (MTA) Study. Figure 1.8 shows the members of the MTA project. Almost 600 children were treated in six university sites by investigators deemed competent in both pharmacological and behavioral management of ADHD. As Eisenberg predicted, the study was designed to test the idea that the combined treatments would be more effective than either treatment alone.

The rationale, design, subject selection, composition of treatments, and major findings for this large, complex long-term treatment of ADHD have been well described by Jensen et al. elsewhere [58]. Suffice it to say, the findings clearly demonstrated the superiority of multimodal therapy, as well as the superiority of the carefully scripted delivery of the drug and behavioral treatments over the usual care found in the community. Long-term follow-up of the initial findings continues to support the value of combined multimodal therapy over single treatment approaches.

**Adult ADHD**

One of the major factors in the recent upsurge of scientific notice of ADHD has been the rediscovery that adults have ADHD. Despite Crichton’s remarkable very early 1798 identification of an ADHD subtype in adults, and Wender’s early revival of the concept, the
diagnosis and treatment of adults still provokes controversy [59, 60]. Possibly this simply relates to a lag in public perception due to the incorrect belief, long held in the literature, that ADHD is a childhood disorder that disappears in adulthood. That error is probably the result of a tradition in which hyperactivity was considered to be the primary symptom; and indeed, hyperactivity does tend to decline with age, but continues to disrupt attention and behavior in the form of mental restlessness. In addition, there are several technical problems in making a diagnosis in adults. These have been succinctly noted by Jensen in a book review [61, p. 97]:

(a) Problems with the accuracy of retrospective recall based on adults’ reports of their childhood ADHD symptoms;
(b) Variations in severity or comorbidity thresholds leading to differing times to diagnosis;
(c) Socioeconomic and family factors that differ across patients and within patients over time;
(d) Discontinuities in who serve as key informants during the childhood versus adult years;
(e) Substantial differences in the tasks of children with ADHD versus adults with ADHD;

(f) Gradual development and accumulation of positive skills in coping with and/or negative consequence of ADHD, and

(g) Vast differences to which children versus adults with ADHD have control over their selection of environments in which ADHD symptoms may be most manifest.

Despite these barriers, research strongly supports the validity of an adult diagnostic category. This research stems primarily from both long-term follow-up of children diagnosed with ADHD, and cross-sectional studies comparing diagnosed ADHD with normal controls and with other psychiatric conditions [62–64].

Barkley and colleagues chose to bypass peer review in order to present a wealth of data from two extraordinary studies, in a manner that was both readable and cogent. While peer-reviewed detailed monographs or journal articles will undoubtedly follow, there seems little doubt that their work firmly establishes the importance of the adult diagnostic category, albeit with important changes needed to rectify shortcomings of the DSM-IV version, particularly the age of onset and number of criteria needed for diagnosis. Though more
complicated by comorbidity and physical status, considerable work also demonstrated the robust effects of stimulant medications for adult ADHD [65–71].

**Non-scientific causes of the rise of ADHD**

Space does not permit an account of all of the *non-scientific* reasons why ADHD has thrived as a diagnosis and treatment over the past several decades, including the many controversial attacks on the concept and its treatments. However, a recent comprehensive and scholarly account by Rick Mayes and colleagues clearly shows the significant impact of several factors [72]:

1. A confluence of trends [clinical, economic, educational, political];
2. An alignment of incentives [among clinicians, educators, policy makers, health insurers, the pharmaceutical industry];
3. The growth in knowledge about ADHD and stimulants;
4. Decreasing stigma associated with mental disorders. [p. 2]

These factors in turn led to changes in assistance through the Supplemental Security Income Program, lobbying pressures from parents of children with ADHD, and the Individuals with Disabilities Education Act (IDEA), and finally expanded eligibility for reimbursement through Medicaid.

As an example of one of the most significant non-scientific influences, it is instructive to examine the impact of the US Food and Drug Administration (FDA) Modernization Act of 1997 on the growth of new drug treatments for ADHD. This act, which extended the patent exclusivity life for new drugs, immediately prompted investment in research on new medication formulations such as long-acting methylphenidate and amphetamine, molecular alterations of older drugs, new uses for older drugs, and promising drugs that had failed in treatment of other disorders (Figure 1.9).

Note the relatively stable lack of interest in methylphenidate and amphetamine for the 15 years prior to the 1997 Act. Cooperation between drug companies and researchers on ADHD was quite limited until it became possible for the major pharmaceutical companies to recoup the investment required to gain approval of a new drug prior to the 1997 Act and then a great burst of activity for the stimulant drug research took place.

**Summary and conclusions**

What accounts for the remarkable increase in the scientific awareness of ADHD with which we began this brief history? Over the course of several centuries a few intrepid and dedicated clinicians made careful observations on children, eventually leading to a relatively clear understanding of those we now diagnose as having ADHD. These clinicians and scientists began with a simple notion of mental disturbances arising from overstimulation, leading to a disordered behavior pattern in children that appeared incongruous given their intellect and upbringing, and immoral according to the standards of the community. From the beginning they saw a neurological basis for the susceptibility to misguided attention and distraction.

This subtle combination of inattention and disordered behavior was from its beginning assumed to be due to either an illness affecting the brain or unknown constitutional factors. But it took “thinking outside of the box,” a shift to a new biomedical paradigm, away from an *etiological* paradigm to a *behavioral* paradigm, before advances could be made in casting the diagnosis specifically enough for real neuroscience to enter the discussion. For instance, at last there was a phenotype that allowed partial confirmation of strong genetic influences [73, 74].
Even so, there is still considerable concern over the heterogeneity of the phenotype provided by DSM-IV. In the future, the search for endophenotypes may eventually provide a more refined set of phenotypes from which more specific causal factors can be discovered [75, 76].

I have argued here that the explosion of scientific interest in ADHD is a cumulative effect of the gradual transformation from the pre-scientific era involving astute observations of clinical details in an etiological framework of mental disorders, to a behavioral framework of the DSM period. During the early period leading up to modern conceptions of ADHD, there was a universal belief that the behavior pattern of ADHD (under other names) was the result of inattention and distraction, caused by a neurologically based deficit. Overstimulation was the key proximate cause of inattention and thus the trigger which revealed the underlying weakness in the ability to inhibit socially inappropriate actions.

I have touched upon some of the non-scientific influences accounting for the explosive attention to the ADHD concept, but believe that an abundance of strong data from neuroscience and clinical trials strongly affirm the role of genuine science in the validity of this concept, and largely accounts for the wide interest in the concept of ADHD. Confirmation of this conclusion from a quantitative point of view awaits the next intrepid scientific historian of science. I have made a slight gesture in the direction of a bibliometric account with a kind of bibliometric of this conclusion from a point of view quantitative

References


