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Review Article

Review Article

The lasting legacy of Charles Fisher (1908–1988), pioneering sleep laboratory scientist and sleep medicine psychiatrist

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Abstract

Charles Fisher is a pioneering historical figure in sleep laboratory research and sleep medicine who distinguished himself in nine areas: (1) he first documented nocturnal sleep-onset rapid eye movement (REM) sleep periods in narcoleptic patients; (2) he published the first case of polysomnography (PSG) documented acute REM sleep behavior disorder (RBD) that was triggered by sudden withdrawal from a monoamine oxidase inhibitor in 1978, 8 years before the formal identification of RBD; (3) he worked with Roffwarg and Dement on the early delineation of the ontogeny of the human sleep cycle; (4) he first demonstrated that benzodiazepine (diazepam) therapy was effective in controlling night terrors together with suppression of stage 4 non-rapid eye movement (NREM) sleep, and he was also an early investigator of night terrors as phenomena emerging from stage 4 NREM sleep, without dreaming, as had been traditionally assumed; (5) he collaborated with another pioneering sleep medicine physician, William C. Dement on studies focused on REM sleep deprivation and dreaming at Fisher's Mt. Sinai Hospital sleep laboratory in New York City; (6) he published the first PSG-documented case of sleep-related (psychogenic) dissociative disorder in 1976; (7) he first documented that typical nightmares ("anxiety dreams") occurred during REM sleep; (8) he conducted some of the earliest research, beginning in 1965, that documented cycles of nocturnal penile tumescence emerging in conjunction with REM sleep cycles; and (9) he conducted similar early studies of female sexual arousal during sleep that occurred predominantly in REM sleep.

Key words: sleep-onset REM periods/SOREMPs; acute REM sleep behavior disorder/RBD; narcolepsy; night terrors/sleep terrors; slow-wave sleep; nightmares; sleep-related (psychogenic) dissociative disorders; REM/dream deprivation and rebound; ontogeny of human sleep; history of sleep medicine

Statement of Significance

Charles Fisher was a pioneer in the early history of sleep laboratory and clinical sleep research. His seminal work included identifying nocturnal sleep-onset rapid eye movement (REM) periods in narcoleptic patients; identifying acute REM sleep behavior disorder triggered by sudden withdrawal from monoamine oxidase inhibitor therapy; identifying sleep-related dissociative disorder; investigating night terrors emerging from stage 4 non-rapid eye movement (NREM) sleep, without dreaming; demonstrating that benzodiazepine therapy controlled night terrors together with suppression of stage 4 NREM sleep; collaborating on REM sleep deprivation studies; first documenting that typical nightmares occurred during REM sleep; etc. Fisher's name and prominence in the history of sleep medicine since his demise have unfortunately been hidden in obscurity, which underscores the importance of presenting his pioneering work herein.

Charles Fisher, MD, PhD is a pioneering historical figure in sleep laboratory research and sleep medicine who distinguished himself by his work in the following nine major advances: (1) he first documented nocturnal sleep-onset rapid eye movement (REM) sleep periods (SOREMPs) in narcoleptic patients, done in his sleep laboratory at Mt. Sinai Hospital in New York City and in the sleep

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laboratory at the University of Chicago [1]; (2) he published the first case of polysomnography (PSG) documented acute REM sleep behavior disorder (RBD) that was triggered by sudden withdrawal from a monoamine oxidase inhibitor (MAOI) in 1978 [2], 8 years before the formal identification of RBD [3]; (3) he worked with Roffwarg and Dement on the early delineation of the ontogeny of the human sleep cycle [4]; (4) he first demonstrated that benzodiazepine (diazepam) therapy was effective in controlling night terrors together with suppression of stage 4 non-rapid eye movement (NREM) sleep [5], and he was also an early investigator of night terrors as phenomena emerging from stage 4 NREM sleep, without dreaming, as had been traditionally assumed [6, 7]; (5) he collaborated with another pioneering sleep medicine physician, William C. Dement, MD, PhD, on studies focused on REM sleep deprivation and dreaming at Fisher's Mt. Sinai Hospital sleep laboratory [8, 9], (6) he published the first PSG-documented case of sleep-related (psychogenic) dissociative disorder (SRDD) in 1976 [10]; (7) he first documented that typical nightmares ("anxiety dreams") occurred during REM sleep [11]; (8) he conducted some of the earliest research, beginning in 1965, that documented cycles of nocturnal penile tumescence emerging in conjunction with REM sleep cycles [12]; and (9) he conducted similar early studies of female sexual arousal during sleep that occurred predominantly in REM sleep [13].

Fisher was born in Los Angeles in 1908, and did several years of undergraduate work at the University of California, Southern Branch (now UCLA), subsequently finishing his bachelor's degree at the University of Chicago with a major in psychology. He began medical school at the University of Chicago in 1931, doing his medical training on a part-time basis and graduating in 1939. Simultaneously, in 1932 he began a fellowship at S. W. Ranson's Institute of Neurology at Northwestern, working in physiology/neurophysiology. He obtained his PhD there in 1934, doing important research on hypothalamic lesions that can cause diabetes insipidus, with the findings eventually published in a book [14]. He continued his research in this laboratory after receiving his PhD, focusing on hypothalamic-hypophyseal control of pregnancy, labor, and sexual behavior, for which he published numerous papers. These experiences were clearly important in determining his affinity for experimental approaches and interest in the physiological dimensions of sleep and dreaming.

After he graduated from medical school, he did a 2-year internship at St. Elizabeth's Psychiatric Hospital in Washington, DC. During World War II, he was drafted into the Public Health Service where he worked on the neuropsychiatric service of the Marine Hospital on Ellis Island, seeing many patients with "war neuroses" and fugue states.

Dement first contacted Fisher in 1955 and they began a correspondence. In 1957, Fisher invited Dement to Mt. Sinai Hospital to do an internship, and following that they obtained grant funding and set up a sleep laboratory [15]. They began by doing the REM deprivation experiments, at that time thought of as "dream deprivation" [8, 9].

Fisher was a Clinical Professor of Psychiatry at the Mt. Sinai School of Medicine in New York City. He was a dedicated psychoanalyst who maintained a clinical practice alongside his research activities and served from 1965 to 1967 as president of the New York Psychoanalytic Institute. For Fisher, the clinical and research aspects of his work were always closely linked. He made unstinting, comprehensive efforts to integrate the new findings in sleep/dream research with the psychoanalytic theory available to him at that time [16]. Figure 1 is a photograph of Charles Fisher.

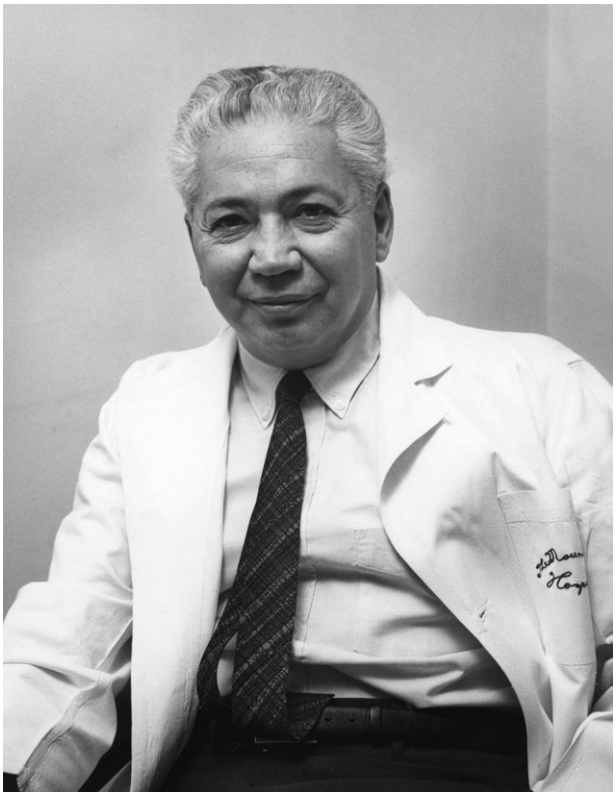

Figure 1. Photograph of Charles Fisher (courtesy of his daughter Barbara Fisher).

It is important to differentiate Charles Fisher, the pioneering sleep researcher and psychiatrist who is the subject of this review, from his contemporary Charles M. Fisher (also known as C. Miller Fisher), a noted neurologist who had published the pedagogic piece on "Fisher's Rules" consisting of 17 "rules" that comprised basic principles he had followed in the practice of medicine [17]. [These rules were originally written by the noted Harvard neurologist Louis Caplan.] Also, Charles M. Fisher (1913–2012) had his obituary published in the Archives of Neurology/JAMA Neurology [18]. His peer-reviewed publications can be found in PubMed and Google Scholar, in contrast to the sleep researcher and psychiatrist Charles Fisher whose work cannot be accessed through these same resources, underscoring the need to call attention to his pioneering work in this review of his career. Finally, the Charles Fisher we are discussing herein, should also be distinguished from Charles P. Fisher (born in 1946), the contemporary psychiatrist/psychoanalyst with a major focus on neuroscience who is located in Berkeley California.

A book chapter written by Charles Fisher that was published in English in the USSR in 1978 contains substantial original material supporting the important historical role played by Fisher in sleep laboratory research and sleep medicine [2]. Since the Metsniereba Publishing House existed from 1968 until 1989 when it was shut down permanently (confirmed by Google search), we can now extract pertinent sections of this historically important book chapter without copyright infringement, in order to allow the seminal work of Fisher to be broadly available to current and future readers. Also, this chapter in its entirety has been scanned and is available in Supplementary Material A. [Comment: Although

Fisher grouped enuresis with night terrors and somnambulism as disorders of arousal from NREM stages 3 and 4 (delta wave) sleep, reflecting the early conception of enuresis, sleep enuresis is no longer classified as a Disorder of Arousal in the current sleep diagnostic classification system.]

The pioneering research by Charles Fisher will now be described.

1) Nocturnal SOREMPS in Narcolepsy: Fisher was the senior author of the first published study on nocturnal sleep in narcoleptics that was conducted in his sleep laboratory and that at the University of Chicago, together with two other historic sleep research figures, viz. Allan Rechtschaffen and Wiliam C. Dement [1]. Nine narcoleptics (6 men, 3 women; 6 with cataplexy, 5 with sleep paralysis [SP], and hypnagogic hallucinations [HHs]), underwent 1–3 PSGs for a total of 18 PSGs. There were three notable novel findings: (i) SOREMPs were "the most striking result of this study" that was found in 7/9 narcoleptics, with a mean SOREMP length of 15.6 min (range, 6–33 min), and with dreaming reported in four awakenings (two spontaneous, two experimenter-induced). In contrast, none of the nine controls had a SOREMP. These SOREMPs in narcoleptics were identified as "a distinctive phenomenon which is virtually unknown in other pathological conditions or in normals." [Footnote: Vogel had earlier (1960) documented SOREMPs occurring in a narcoleptic patient during daytime naps [19]. Interestingly, Vogel's patient had been withdrawn from amphetamine treatment 2 days prior to the sleep recording, so his important finding may in that instance have been an artifact of drug withdrawal and consequent REM rebound]. Fisher et al. also indicated that daytime sleep attacks in narcoleptics could represent SOREMPs, and also suggested that SP and HH could represent REM sleep intrusion phenomena. (ii) Narcoleptics had significantly increased body movements during sleep compared to controls, scored as mean movements per hour of sleep: 9.5 (±2.9)/h vs 5.3 (±1.8)/h, $p = 0.02$. (iii) There was no difference in sleep architecture (including NREM–REM cycling) apart from the SOREMPS between narcoleptics and controls.

Comments by the authors (C.H.S., F.P., and A.S.E.): Fisher's legacy from this study is found with SOREMPs during nocturnal PSGs being one of the core diagnostic criteria for narcolepsy contained in the ICSD-3-TR [20]. Also, another legacy from this study was reflected in Fisher's strong suspicion that daytime sleep attacks in narcoleptics could represent SOREMPs, which is confirmed by the SOREMPs requirement in multiple sleep latency tests for diagnosing narcolepsy [20].

2) Acute RBD: Fisher published the first case of acute RBD that emerged during intense REM sleep rebound triggered by sudden withdrawal from high-dose MAOI therapy (with total REM suppression) in the successful therapy of amphetamine-resistant narcolepsy type 1 in a 58-year-old man (pages 81–85) [2]. Emphasis on acute RBD is provided by italics, along with a comment about his collaboration with William C. Dement:

"A 58 year old man had suffered from sleep attacks for 40 years. (*He was first studied by Dement and myself …. and was probably the first narcoleptic investigated in a modern sleep laboratory*.) He was constantly fired from jobs because of falling asleep, in spite of the fact that he was on heavy doses of amphetamines. Additionally, he had quite frequent attacks of cataplexy triggered by his telling aggressive jokes or making a hostile remark….The patient was put on Nardil (phenelzine) with doses up to 75 or 90 mg daily and over nine months showed total suppression of REM sleep…We were able to bring about a near complete disappearance of both his cataplexy and narcoleptic attacks…Prolonged and total REM period suppression did not produce psychosis and there were no obvious behavioral disturbances."

"Following rapid withdrawal of the drug, a toxic psychosis or delirium with hallucinations and delusions occurred during rebound. *During drug withdrawal REM percent gradually increased and on the fourth night when there was 60% REM sleep, and presumably because of tremendous REM rebound pressure, the patient had a number of severe nightmares with verbalization and cries for help. Suspension of motor paralysis with return of muscle tone resulted in the subject acting out his dreams (Figure 12). Thus, he had a nightmare about his brother pushing him out of the car and felt himself repeatedly falling. He was found lying on the floor and said he had fallen out of bed five times, the number of times his brother had pushed him out of the car.*"

"The following day…at the beginning of the sleep period, for more than an hour he had brief periods of REM sleep with hallucinations alternating with cataplexy…and the motor barrier was breached and the patient was acting out his dreams. He made running movements, actually got up and tried to open the door, gestured and pointed and these movements were temporally associated with dream content."

"In order to terminate the developing delirium, the patient was given 75 mg Nardil (phenelzine). Within five days REM sleep reached zero, where it has remained, and psychotic symptoms quickly disappeared."

"Although total REM suppression does not appear to cause psychosis, psychosis can come about during rebound following rapid withdrawal of Nardil and following withdrawal of other REM suppressing drugs such as alcohol and barbiturates, providing the rebound is great enough…*When this occurs, motor paralysis is breached, muscle tone is regained and dreams are acted out*. Thus, the so-called REM intrusion or spill-over theory of drug withdrawal psychosis or acute delirium first proposed by Dement and myself, and elaborated by Gross et al., Greenberg and Pearlman and Feinberg and Evarts, is supported."

Comments by the authors (C.H.S., F.P., and ASE):

A) From our current perspective, this case contains the following four known risk factors for RBD: older age (58 years old); male gender; narcolepsy-cataplexy [21]; and rapid withdrawal from total REM sleep suppression, with massive REM rebound, from sudden discontinuation of the MAOI medication that previously had completely suppressed REM sleep.

B) Fisher did not coin any specific term in describing acute RBD, but rather used accurate descriptive language in reporting his findings.

C) A recent comprehensive review of acute and subacute RBD [22] provides a greatly expanded list of triggering conditions that build on the original case reported by Fisher, along with several other early cases dating back to 1966, as reviewed [22]. Various medications, substance use/abuse, and abrupt drug withdrawal states have been identified. Also, structural brain lesions (tumors, vascular, demyelinating disease, autoimmune disease, paraneoplastic disease, and postsurgical), especially in the pontine region may cause acute RBD. In addition, RBD can appear acutely after a stressful life event and in post-traumatic stress disorder. As stated by the authors [22], RBD recognition in all these acute/subacute conditions has both clinical value and also value in more

deeply understanding the pathophysiology of RBD across different clinical scenarios.

3) Delineation of the Ontogeny of the Human Sleep Cycle from Infancy to Old Age: With Howard Roffwarg and Dement, Fisher studied the development of the sleep cycle over the course of the entire human life cycle [4]. This included observations of neonates at the nurseries at the University of Chicago Lying-In Hospital and Columbia Presbyterian Hospital in New York. They confirmed Aserinsky and Kleitman's finding of an alternation of periods of active and quiescent sleep in infants, with a cycle length of 50–60 min, and went beyond the earlier authors in verifying that REMs are present during the periods of active sleep. They also noted sleep-onset REM periods in infants. Important longitudinal childhood developmental changes that were reported included the lengthening of the NREM/REM cycle, a decrease in the very high percentage of REM (active) sleep seen in neonates, gradual suppression of motor activity during REM sleep, and the appearance with development of differential patterns of REM sleep and delta sleep across the night, with the REM periods lengthening over the course of the night and most of the delta sleep being seen in the early NREM periods. More subtle changes were reported over the years of adulthood.

4) Seminal Clinical and PSG Studies on Night Terrors and Their Therapy: Fisher first reported the benefit of benzodiazepine (diazepam) therapy in controlling (severe) night terrors in tandem with suppression of stage 4 NREM sleep as the presumed mechanism of therapeutic action [5]. He was also an early investigator of night terrors emerging from stage 4 NREM sleep, without dreaming [5–7], as previously had been assumed. This work built on, and expanded, the previous seminal work on NREM parasomnias by Broughton as being disorders of arousal from deep NREM sleep [23], and by the Kales group on somnambulism being a disorder of deep NREM sleep [24].

Pertinent sections on this topic in Fisher's book chapter [2] are presented in Supplementary Material B.

5) Collaboration with William C. Dement on REM Sleep Deprivation and Dreaming Studies at Fisher's Sleep Laboratory.

As reported in the Psychiatric News, published by the American Psychiatric Association in 2004 [25], after William C. Dement, MD, received his PhD at the University of Chicago in 1957 "he went to Mt. Sinai School of Medicine in New York City to work with Charles Fisher, MD, a psychoanalyst and dream researcher. One of Dement's studies there showed people deprived of 'dreaming', that is, sleep in which REMs occurred, preferentially recovered it when next permitted to sleep." Dement subsequently went to Stanford University where he established the renowned narcolepsy research program and clinical sleep medicine program.

Although Dement and Fisher's original hypothesis that people deprived of "dreaming" would develop psychosis was not confirmed, they discovered that the longer subjects were deprived of REM sleep, the more frequent attempts they would make to enter REM sleep, and on recovery nights they demonstrated the important phenomenon of "REM rebound," including significant increases in REM sleep time and percentage [8, 9]. The Fisher–Dement collaboration on this topic from Fisher's book chapter (pages 76–77) [2] is contained in Supplementary Material B.

6) First PSG-Documented Case of SRDD.

Fisher was also a pioneer in SRDD, reporting the first case in 1976 [10]. SRDD is a psychiatric parasomnia that was formally identified in a series of eight cases published in 1989 [26] (and republished in 2021 [27]), and then incorporated within the Parasomnias section of the ICSD-2 [28]. There has been a growing number of documented cases of SRDD over recent years that have expanded the knowledge base of this still under-recognized parasomnia [26, 29–33]. The core feature of SRDD involves psychogenic dissociative episodes during alpha-EEG activity emerging in wake–sleep transitions, or after awakenings from N1, N2, or (less frequently) REM sleep. The abnormal behaviors typically occur non-abruptly, i.e. up to 30–60 s after the onset of alpha EEG activity, in major contrast to disorders of NREM arousal in which the abnormal behaviors occur with the arousals, usually from N3 sleep [20]. Furthermore, nearly all reported cases involve histories of past and/or current abuse with major psychic trauma (often resulting in PTSD), and with dissociative episodes usually also occurring during the daytime, with SRDD episodes typically replicating the daytime dissociative episodes.

Fisher's seminal case of SRDD from 1976 [10], which captures all the major features of SRDD, is summarized in Supplementary Material B.

Comments by the authors (C.H.S., F.P., and A.S.E.):

In Fisher's SRDD case, psychologically meaningful sleeptalking occurred during the patient's dissociated states, which is distinct from typical random-content sleeptalking in which, as stated in the ICSD-3-TR, "the content of sleep talking has not been shown to reflect actual prior waking behavior or memories" [20].

Also, this case contains elements of dissociative episodes arising from both daytime sleep and nocturnal sleep similar to a recently reported case of SRDD associated with dissociative identity disorder and hypersomnia [31] in which both conditions responded to modafinil therapy, encouraging future study of modafinil as (adjunctive) therapy for dissociative disorders.

7) Documentation that typical nightmares ("anxiety dreams") occur during REM sleep, in contrast to the night terrors of stage 4 NREM sleep [2, 11]. (The authors also described an intermediate intensity of frightening arousal occurring out of stage 2 sleep.)

8) Documentation of recurrent cycles of nocturnal penile tumescence emerging concomitant with REM sleep cycles [12]. This work, done at roughly the same time as Ismet Karacan's group at Baylor in Houston, added to the understanding of the widespread physiological limbic arousal that accompanies REM sleep.

9) Documentation of cycles of female sexual arousal with vaginal engorgement, by utilizing vaginal thermo-conductance, that occur predominantly during REM sleep, and are analogous to male cyclical REM sleep erections [13].

Additional Historical Comments

Another pioneering sleep research investigator needs to be recognized with the very early descriptions of presumed RBD, besides the acute RBD from MAOI withdrawal described by Fisher herein. Irwin Feinberg, in his 1965 article describing sleep in several male DSM-II defined "chronic brain syndrome" patients [34], reported REM sleep abnormalities that bear a strong similarity to RBD.

Feinberg stated, on page 23, that "Dream periods frequently ended in behavioral arousal….These subjects repeatedly awoke disoriented and with a fixed idea—that it was urgent that they catch a train, or get to work, etc.—on which they attempted to act… the awakenings were not gradual but dramatically sudden." This quoted description strongly suggests RBD in dementia patients, most likely (from our current perspective) suffering from an alpha-synucleinopathy. Furthermore, also in 1965, Feinberg published a different case of an elderly, hallucinating male patient who was explicitly Parkinsonian, as described on page 1019, who underwent PSG 14 days after achieving a drug-free state, which showed over four consecutive nights a robust REM%s ranging from 30% to 37% [35]. Of particular relevance in this case was the description of hostile behavioral enactments originating upon awakenings from sleep in an otherwise docile, polite, and "courtly" man. Therefore, Feinberg's pertinent and astute observations on presumed RBD also need to be recognized, as they certainly were a part of the same intellectual zeitgeist of the 1960s in which pioneering sleep medicine and sleep laboratory psychiatrists were fascinated by nocturnal REM-related behavioral phenomena.

Finally, in regards to the historical perspective on the life of Charles Fisher provided by Kenneth Miller [15], the footnotes for Chapters 7–9 of that book relied upon an interview of Fisher by Arnold D. Richards, MD, with the interview sent directly to Miller by Richards' wife (personal communication); it was not available online at the time that Miller was writing the book. However, the transcript of that interview is now available online [36].

Conclusion

Charles Fisher was a meticulous pioneering sleep laboratory and clinical investigator of the manifold sleep-related conditions described herein, including his collaboration with another pioneering sleep medicine scientist and physician, viz. William C. Dement, and the pioneering sleep laboratory investigator, viz. Allan Rechtschaffen. His contributions to our field helped establish important lasting foundations and a lasting legacy that can be appreciated from our contemporary perspectives. It is most impressive what a multi-talented, creative, and productive man Fisher was: "small, dapper, and fiercely brilliant" [15].

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

Acknowledgments

One of the authors (A.S.E.) provided the book chapter written by Charles Fisher described herein (reference 2). Alon Avidan and Bev Hope kindly provided assistance with reference 15. Kenneth Miller (author of the book cited as reference 15) kindly provided the contact information for Barbara Fisher, daughter of Charles Fisher, who then provided the photograph of Charles Fisher shown in Figure 1. Linhoff Photo + The Print Refinery (St. Louis Park, MN) scanned, enhanced, and digitized the photograph of Charles Fisher (Figure 1).

Author Contributions

Carlos H. Schenck (Conceptualization, Formal analysis [equal], Writing—original draft [lead]), Federica Provini (Conceptualization, Writing—review & editing [equal]), and Alan S. Eiser (Conceptualization, Writing—review & editing [equal])

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