表 3　小中高校生の睡眠時間の変化

	小 3・4	10 歳以上の小学生（小 5・6）	中学	高校
2006		8 時間 24 分	7 時間 14 分	6 時間 31 分
2004	8 時間 51 分	8 時間 46 分	7 時間 25 分	6 時間 33 分
2000		8 時間 43 分	7 時間 51 分	6 時間 54 分
1996	9 時間 2 分	8 時間 51 分		
1981	9 時間 24 分	8 時間 56 分		
1965		9 時間 22 分	8 時間 37 分	7 時間 50 分

資料：全国養護教員会（2006），中央教育審議会（2004），NHK 放送文化研究所（2000，1965），日本学校保健会（1996，1981）

ている睡眠相後退型であっても，その有症率はせいぜい 0.1 ～ 0.4%である[3]．また，リズム障害を病名とするには，それが第一義的な要因である必要があるが，現在の子どもたちが必要な睡眠時間を保証されているとは言いがたい（表 3）．また睡眠相後退型の概日リズム睡眠障害については，思春期に顕著になる生活習慣に関連した睡眠相の遅れが混同されて，過剰に診断されているとの指摘がある[4]．

次に「不眠」の観点から見ると，睡眠呼吸障害，睡眠時驚愕症，睡眠関連運動異常症は眠りを阻害し，不眠をもたらす．しかし，これらの有症率は，それぞれ 2.2 ～ 4.8%，1 ～ 6%，睡眠関連運動異常症のうちレストレスレッグズ症候群で 1%，周期性四肢運動異常症で 7.1%程度である[3]．また，「眠気」の観点からは中枢性過眠症の代表であるナルコレプシーが重要となろうが，その頻度は 0.03%[3] である．

以上いずれもが，約 4 人に 1 人の中高生が不眠を訴え，5 割を越える小中高生が昼間に眠気を訴えている現状を説明する病名とはいえない．筆者は現在の日本の子どもたちの大半が該当する病名は，ICSD-2 にしたがえば，「不適切な睡眠衛生」に基づく不眠がもたらす「睡眠不足症候群」と考えている．

Ⅱ　不適切な睡眠衛生と睡眠不足症候群

不適切な睡眠衛生は適切な睡眠衛生（朝日の受光，昼間の心身の活動，規則的で適切な食事，夜間の適切な睡眠環境（暗さ，静けさ，温度，湿度））からの逸脱による不眠で，カフェインやアルコールといった不適切な薬物使用も該当する．

睡眠不足症候群は正常な覚醒状態を維持するために必要な夜間の睡眠をとることが出来ず昼間に眠気が生じる状態で，患者自身は慢性の睡眠不足にあることを自覚していない．症状としては攻撃性の高まり，注意・集中力・意欲の低下，疲労，落着きのなさ，協調不全，倦怠，食欲不振，胃腸障害などが生じ，その結果さらに不安や抑うつが生じる場合もある．特徴としては睡眠を十分とれる週末や休暇時には症状が軽快することが挙げられる．

両者の対策の基本は睡眠衛生の基本（朝の受光，日中の活動の保障，睡眠環境の整備）を踏まえて，適切な時間帯に適切な睡眠時間を確保することに尽きる．すると現在の日本の子どもたちが陥っている状態は単なる睡眠不足ということになる．では対策は睡眠時間の確保，となるが，社会的要因によるのみならず，治療上もこれが実に困難である．睡眠不足解消に「夜ふかし」を改善すればよいという理屈だが，「夜ふかし」の改善そのものが極めて困難である．そこで筆者は，不適切な睡眠衛生と睡眠不足症候群という既存の睡眠関連病態にとどまらない新たな疾患概念の導入が，今不眠と眠気の悪循環に陥っている日本の子どもたちの救済に重要と感じるにいたった．そして，朝型夜型の行動特性とその神経学的背景に関心を寄せるにいたった．

Ⅲ　朝型夜型

1．行動特性

朝型夜型に明確な定義はないが，臨床的な評価尺度としては Morningness-Eveningness Questionnaire Score や Composite Scale of Morningness があり，これらを用いて朝型夜型を判断し，行動上の諸問題との関連が検討されている．原田[5] は朝型夜型と以下の 4 点（①気分が落ち込むことがある，②すぐに怒り出すことがある，③イライラすることがある，④キレて，みさかいがなくなってしまうことがある）との関係を中学生 613 名と大学生・専門学校生 367 名とで調査，夜型傾向の度合いが強まるほど，②怒ると，③イライラの項目の頻度が増し，中学生では就床時刻が遅くなるほど，①落ち込むと，③イライラの項目の頻度が高まるという．思春期では夜型と moodiness（気難しさ，むら気，不機嫌）との関連が特に男子で強く[6]，夜型は入眠困難，短い睡眠時間，朝の気分の悪さ，日中の眠気と関連しており[7]，夜型では日中の昼寝が多く，朝型よりも行動上あるいは感情面での問題点を多く抱え，自殺企図，薬物依存も多く，夜型の度合いが高いほど衝動性という[8]．夜型は男児では反社会的行動，規則違反，注意に関する問題，行為障害と関連し，女児では攻撃性と関連し[9]，夜型では朝型よりも学力が低く[10]，生活リズムが不規則[11] という．朝型で規則的な生活を送ることで，ヒトは機能的に行動できそうだ．ではなぜ朝型がヒトに機能的行動をもたらす可能性が高いのであろうか？

2．朝の光のメリット

朝の光は大多数のヒトで周期が 24 時間よりも長い生体時計の周期を短縮して地球時刻に同調させる[12]．朝の受光をせず，この同調作用が発揮されないと，体内で作動している概日リズムを呈している様々な生理現象が同調されずにそれぞれが個別に活動する．これが desynchronization ―脱同調で，同様の状態は時差ボケでも生じ，意欲低下，覚醒度や作業能率の低下，あるいは状況判断の誤りや胃腸症状などの生理的あるいは知的な面で問題点が生ずる[13]．同様の症状は季節性うつ病[14] や宇宙飛行士[15] にも認める．

また，朝の光は内因性のセロトニン活性を高める[16]．セロトニンは脳内の神経活動の微妙なバランスの維持に重要で，種々の動物実験で，セロトニン系の活性の低下と攻撃性や衝

動性の高まりや社会性の低下との関連が指摘されている[17]．攻撃性や衝動性，自殺企図を特徴とする低セロトニン症候群を提唱する研究者もいる[18]．セロトニンの活性が低下すると，気分が滅入り精神的に不安定にもなる．なお，セロトニン系の働きはリズミカルな筋肉運動（歩行，咀嚼，呼吸）でも高まる[19]．

朝の受光で，セロトニンの活性化とともに生体時計の同調が容易となり，内的脱同調に陥る危険は軽減する．その結果昼間の活動量が増加すると，脳由来神経栄養因子，セロトニン活性増加を介して学習機能が向上，感情制御に好影響が及ぶ．昼間の活動は就床時刻を早め，日中の受光量増加を介して夜間メラトニン分泌量を増加させる．メラトニンは夜間睡眠を容易にし，その抗酸化作用による全身への好影響も期待できる．結果的に睡眠時間が確保され，睡眠不足に伴う種々の不都合からも回避される．これらが朝型が機能的に活動できる背景のメカニズムの一部であろう．

2004年に東京民研学校保健部会が発表した中学生の疲労自覚調査結果で，訴えのあった症状は多い順に，眠い，あくびが出る，横になりたい，といった眠気，疲労関連の訴えに続いて，ちょっとしたことが思い出せない，熱心になれない，考えがまとまらない，いらいらする，物事が気にかかる，肩がこる，腰が痛いであり，これらの症状は20%以上の中学生が訴えていた．すなわち，眠気と不眠のみならず，意欲低下，覚醒度や作業能率の低下，あるいは状況判断の誤りなどを今の中学生は示しているわけで，同様の症状は脱同調，時差ぼけ，季節性うつ病，あるいは宇宙飛行士にも生じ，かつ低セロトニン状態の存在をも示唆する．

筆者らは5歳児の睡眠覚醒リズムの整不整が三角形模写という脳機能に影響し，かつ問題行動（感情面の問題〔物への異常な執着，説明が困難な攻撃性（突然隣の子をたたくなど）〕，交互運動と姿勢保持の問題〔手を振って歩くことができない，ひじにもたれたりしてまっすぐに座れない〕）の発現にも関連することを報告した[20]が，この報告は，眠気・不眠を明確に訴えているわけではない5歳児の知的側面，感情面，身体機能面にも，小中高生類似の問題が生じている可能性を想定させる．

3．夜の光のデメリット

夜の光は朝の光とは逆に生体時計の位相を遅延させ[17]，メラトニン分泌を抑制する[21]．成熟マウスを恒常的な明環境におくと，視交叉上核の神経細胞個々のリズム形成能は失われないものの，神経細胞同士のリズムの同調が困難となる[22]．さらに夜間の受光が生体時計の機能を停止させることも最近明らかにされた[23]．

4．夜型では

「夜ふかし朝寝坊」すなわち夜型は時差ぼけ状態をもたらし，運動量の低下と肥満を招く．その結果セロトニン系の活性が高まらず，イライラ感，攻撃性の増加など感情制御の問題が生じる．運動量が減ると，睡眠不足ともあいまって知的な機能も低下する．さらに「夜ふかし」は，運動不足，睡眠不足，メラトニン分泌低下，肥満ともあいまって，様々な生活習慣病をもたらす（図2）．

Ⅳ　従来の概念との比較

以上を包括すると，夜型となった我が国の子どもたちは，抗し難い大きな社会的要因の影響の下，眠気と不眠を訴え，知的側面，感情面，身体機能面にも問題が生じる病態に苛まれている，と言えよう．実は類似の症状（攻撃性の高まり，注意・集中力・意欲の低下，疲労，落着きのなさ，協調不全，倦怠，食欲不振，胃腸障害，不安，抑うつ）はリズム障害を伴う起立性調節障害[24]，慢性疲労症候群，burnout，vital exhaustion，線維性筋痛症候群，抑うつ状態（気分変調性障害，他の気分障害，抑うつ気分を伴う適応障害）[25]でも認める．

慢性疲労症候群について筆者は，擬似時差ぼけとの共通点を鑑み，慢性疲労症候群をリズム障害の観点から検証してゆくことの必要性を指摘した[26]が，小児慢性疲労症候群研究班もその発症にサーカディアンリズムの持続的な脱同調の存在がポイントとなるとしている[27]．慢性疲労症候群と異同が問

図2　夜ふかし朝寝坊がもたらす心身の諸問題

題となる概念に burnout がある．その臨床的特徴は過度の持続する疲労，感情面の問題，認知機能障害で，慢性疲労症候群のほか，うつ病あるいは vital exhaustion との異同も議論されている[28]．Burnout では不安が強く気分が滅入るといった感情面の症状や，認知機能の問題が中心として捉えられ，発症機転に眠りの問題（睡眠効率の低下，睡眠中の中途覚醒の増加，休日にも眠気が取れないなど）が一義的に大きく関わっている可能性が指摘されている．Vital exhaustion は気力の消失，イライラ感の増大，道徳観喪失，さらには心血管障害の危険因子となる点に関心が寄せられている疾患概念だが，発症のきっかけに夜間睡眠時間が短く，日中の眠気が多いことが指摘されている[29,30]．線維性筋痛症候群では全身にひろがる筋肉・骨の痛み（筋線維，靱帯，腱などが広くおかされ，筋肉が伸ばされ痛む）に焦点が当てられているが，やはり眠りに問題（熟睡感がないこと）が発症のきっかけとして指摘されている[31]．さらに慢性疲労症候群での SSRI[32]，線維性筋痛症候群での SNRI[33] の効果も報告されている．

筑波大学新井邦二郎教授による小学生 3,300 人に対するアンケート調査で，「いつもそうだ」という回答で多かった項目が，よく眠れない（16.8%），やろうと思ったことがうまくできない（15.5%），すごく退屈な気がする（11.8%）であったという．この結果は小学校 4 ～ 6 年生の 1 割が抑うつ傾向，と解釈された（日本経済新聞 2004 年 7 月 6 日）．北海道の小中学生でもうつに関する大規模な調査が，傳田健三北海道大学助教授を中心に国際的な診断基準に基づいて行われ，3,331 人から回答が得られ，全体の 13%（中学生の 22.8%，小学生の 7.8%）が，「うつ傾向」と判断されたという（読売新聞 2005 年 2 月 22 日）．質問項目には「楽しみにしていることがたくさんある」「とてもよく眠れる」「食事が楽しい」「泣きたいような気がする」「生きていても仕方ないと思う」などがあり 3 択で回答するのだが，これら「うつ傾向」とされる場合の症状もこれまで述べてきた症状と重なる．

むろんこれらの病態にはそれぞれ特有の発症要因がある．

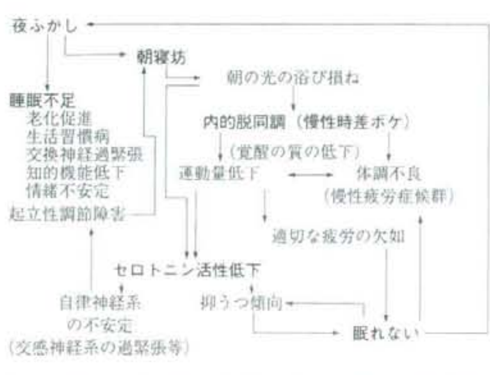

図 3　夜ふかしがもたらす低セロトニン状態と関連疾患

たとえば，慢性疲労症候群について言えば，小児期に運動量の少ないこと[34]，小児期のネグレクトも含めた性的・身体的・精神的外傷や様々な精神的病態（うつ，不安，心的外傷後ストレス）[35] も発症の危険因子に挙げられている．しかし，burnout，vital exhaustion，線維性筋痛症候群では発症のきっかけに眠りの問題が多いことは，すでに述べた通りである．不規則な生活をしていると体温リズムの振幅が小さくなり，振幅の小ささは「うつ」症状の亢進と関係するという観察もある[36]．これらの診断名は，それぞれ特有の観点から診ることで，各々の診断が下されていると言う側面があろう．

V 失 同 調

筆者は前章で紹介した種々の病態の背景に「夜ふかし」が一義的に問題を惹起する一群が存在し，その背景に低セロトニン状態が存在するとの仮説を提唱（図 3）[37]，その後この仮説を支持するいくつかの傍証も提出した．朝寝坊，夜ふかしな幼児での CBCL 得点高値[38]，早起きでの日中の活動量増加[39]，登校困難者での ATNR 上昇[40] である．生活習慣病，キレる子のほか，起立性調節障害，慢性疲労症候群，抑うつ気分も専門家のみの問題ではない．身近な家庭環境，保育環境，生活習慣，しつけの見直しで対応できる部分も一部には必ずあるのだという認識の必要性からの提起であった．

しかし，繰り返すが，現在の日本の子どもたちが陥っている病態は，「夜ふかし」のみを改善すれば治癒するほど単純ではない．「夜ふかし」の改善そのものが極めて困難な状態に陥っている．「脱同調」はさまざまな概日リズムを呈する生理現象の相互関係が破綻した状態（位相の不一致）を示す，基礎医学的な基盤を有する文言である．そこで筆者はあくまで臨床的側面を重視し，多くは「夜ふかし」がその発端となり，容易に悪循環に陥り，低セロトニン状態からの離脱が困難な病態を，新たな臨床的概念として提唱する必要性を感じるにいたった．

その本質は概日リズムを呈する様々な生理現象のリズムの破綻（周期，相互性，振幅など）で，症状は睡眠覚醒リズム，ホルモン分泌，消化器機能などの自律神経機能の異常にとどまらず，攻撃性の高まり，注意・集中力・意欲の低下，落着きのなさ，協調不全，疲労，倦怠，不安，抑うつなど高次脳機能，身体機能の異常，さらには精神症状をも，多くはおそ

表 4　失同調

本質：	概日リズムを呈する様々な生理現象のリズムの破綻（周期，相互性，振幅等）
原因：	夜間受光と朝日の受光喪失（夜ふかし朝寝坊）
症状：	自律神経機能（睡眠覚醒リズム，ホルモン分泌，消化器機能等）の異常，高次脳機能異常（知的低下，協調不全，社会性低下等），神経症状（注意・集中力・意欲の低下，攻撃性の高まり，落着きのなさ等），身体機能異常（疲労，倦怠等），精神症状（不安，抑うつ等）等
予後：	初期には機能的であった脳の障害も一部は固定化し，長期化し，悪循環からの離脱がますます困難となる場合がある．

らく二次的に，一部は一義的にも，もたらすと想定した．さらに，特に発育過程でこの病態が長期化することで，初期には機能的であった脳の障害も一部は固定化し，長期化し，悪循環からの離脱がますます困難となり，通俗的には「ひきこもり」あるいは，「ニート」と称される状態とも関連する病態をもたらす可能性も想定している．そこで名称としては，その本質が自律神経系のみならず，多岐にわたる様々な系に空間的のみならず，時間的にも生ずるリズム障害であるとの仮説のもとに，asynchronization（失同調）と称することとした（表4）．

ある種のカビに温度と光の条件を整えると，その個体が概日周期を失う singularity と呼ばれる現象が引き起こされる[40]．最近になってマウスの皮膚細胞を用いての実験で，夜間の光がこの現象を引き起こすことが報告された[23]．夜間の光には生体時計の位相を変化させるだけではなく，singularity を生じさせる作用があることが示されたわけである．まさに仮説として提唱した asynchronization（失同調）が，夜間の光によって引き起こされる機構の本質に迫る実験成果といえよう．概日リズム睡眠障害の時差型について，教科書にも「障害の程度には個人差も大きい」[13]，とあるが，同じ環境でもこれまで述べてきた諸症状を呈する場合も呈さない場合もある．訴えとなる症状に微妙な差異もある．これらは失同調が引き起こされる機構の感受性，その他の個体差で説明が可能になると想定している．

おわりに

「はじめに」の項で小中高生が寝不足の原因として「眠れない」を挙げていることを紹介した．この語句をそのまま捉え，最近しばしば聞くのが「睡眠障害の増加」という指摘である．しかし，昼間は身体を動かさず，夜はいつまでも明るいディスプレイの前で過ごしていては，身体は疲れず，メラトニン分泌は抑制され，生体時計の位相は遅れ，生体時計の機能は停止し，夜になったからといって眠れないのは当然である．ヒトという動物の生理を考えれば至極当然の生理現象の結果の，不適切な睡眠衛生に基づく「眠れない」のである．しかし，現実にはこのようないわば生理的な当然，生じるべくして起こっている不眠もしばしば「睡眠障害」と診断され，薬物投与すら行われている．消化不良で下痢をしているにもかかわらず飽食し，そして下痢止めを求めているようなものである．眠りに関する基礎的知識の欠如が，「疾病」とされる状態を造成しているのではなかろうか．眠りに関する基礎的な知識の周知がきわめて重要である．

失同調という新たな概念のもと，その病態生理の解明とそれに伴い治療法の進歩することを期待する．

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A Novel Proposal Explaining Sleep Disturbance of Children in Japan — Asynchronization

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It has been reported that more than half of the children in Japan suffer from daytime sleepiness. In contrast, about one quarter of junior high-school students in Japan complain of insomnia. According to the International Classification of Sleep Disorders (Second edition), these children could be diagnosed as having behaviorally-induced insufficient sleep syndrome due to inadequate sleeping habits. Getting an adequate amount of sleep should solve such problems; however, such a therapeutic approach often fails. Although social factors are involved in these sleep disturbances, I feel that a novel notion — asynchronization — leads to an understanding of the pathophysiology of disturbances in these children. Further, it could contribute to resolve their problems. The essence of asynchronization is a disturbance of various aspects (e.g., cycle, amplitude, phase, and interrelationship) of the biological rhythms that normally exhibits circadian oscillation. The main cause of asynchronization is hypothesized to be the combination of light exposure during night and the lack of light exposure in the morning. Asynchronization results in the disturbance of variable systems. Thus, symptoms of asynchronization include disturbances of the autonomic nervous system (sleepiness, insomnia, disturbance of hormonal excretion, gastrointestinal problems, etc.) and higher brain function (disorientation, loss of sociality, loss of will or motivation, impaired alertness and performance, etc.). Neurological (attention deficit, aggression, impulsiveness, hyperactivity, etc.), psychiatric (depressive disorders, personality disorders, anxiety disorders, etc.) and somatic (tiredness, fatigue, etc.) disturbances could also be symptoms of asynchronization. At the initial phase of asynchronization, disturbances are functional and can be resolved relatively easily, such as by the establishment of a regular sleep-wakefulness cycle; however, without adequate intervention the disturbances could gradually worsen and become hard to resolve.

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A NOVEL DISEASE CONDITION PRESENTING WITH INSOMNIA AND HYPERSOMNIA –ASYNCHRONIZATION

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Abstract

More than half of the preschoolers/students in Japan have recently complained of daytime sleepiness, while approximately one quarter of junior and senior high school students reportedly suffer from insomnia. These children might suffer from behavioral-induced insufficient sleep syndrome due to inadequate sleep hygiene, and conventional therapeutic approaches often fail. The present study addressed whether asynchronization, a novel clinical notion, could be responsible for the pathophysiology of these sleep disturbances and could provide a better understanding for successful interventions. This clinical concept was designed with special reference to the basic concept of singularity. The essence of asynchronization comprises disturbances in various aspects (*e.g.*, cycle, amplitude, phase, and interrelationship) of biological rhythms that normally exhibit circadian oscillation. These disturbances presumably involve decreased activity of melatonergic and serotonergic systems. The major triggers for asynchronization are hypothesized to be a combination of light exposure during the night, which decreases melatonin secretion, as well as lack of light exposure in the morning, which decreases activity in the serotonergic system. Prevention of asynchronization must include acquisition of morning light and avoidance of nocturnal light. Possible potential therapeutic approaches for asynchronization involve conventional and alternative therapies. We should know more about the property of the biological clock.

Key words: desynchronization; melatonin; serotonin; sleep; circadian rhythm; singularity

1. Introduction

Circadian rhythms are generated in the suprachiasmatic nucleus (SCN). SCN development takes place throughout the course of gestation, remains immature for some time after birth, and is suggested to be vulnerable to maternal influences [1]. Studies have shown that the earlier mothers fell into nocturnal sleep during late pregnancy, the longer the babies slept during the night at one month of age [2]. The same report described that onset time for the longest nocturnal sleep of mothers during late pregnancy was similar to the babies at one month of age, suggesting that synchronization of sleep rhythm begins during late pregnancy. Because circadian rhythm disturbances in the young can impact SCN function during the lifespan, therapeutic strategies are much needed. Nevertheless, very little is understood regarding pathophysiology of circadian rhythm disruption, which makes it difficult to determine the appropriate clinical approach for these patients.

This review article introduces the recent phenomenon of a nocturnal lifestyle among Japanese youth, and the association between nocturnal lifestyle and behavior. In addition, the presumed involvements of neurological systems such as the biological clock, melatonergic system and serotonergic system in youth that prefer a nocturnal lifestyle are reviewed. Finally, a new clinical entity – asynchronization [3, 4] - has been proposed, in an attempt to elucidate the pathophysiology of circadian disruptions and to provide novel, clinical therapeutic approaches. This clinical concept has been termed with special reference to the basic concept of singularity. Circadian singularity behavior was discovered in 1970, according to observation that specific, dim, blue-light, pulse stimulus, with a unique stimulus time and duration, resulted in disturbed circadian rhythm in Drosophila [5].

2. Insomnia and hypersomnia among Japan youth

2-1. Recent statistics of bedtime and sleep duration

The percentage of 1-year-old children who go to bed later than 22:00 has increased from 25.7% in 1980 to 54.4% in 2000. Similar statistics have also been reported for the rate of 3-year-old children who go to bed later than 22:00: 21.7% in 1980 [6], 43.8% in 1999 [7], 49.8% in 1999-2000 [8], 52.0% in 2000 [6], and 51.1% in 2004 [9].

The rate of fourth-grade students at elementary schools in Tokyo going to bed later than 0:00 has also increased from 0% in 1979 to 2% in 2002 [10]. The mean bedtime in 2004 for elementary school students in the fifth and sixth grade was 22:03, junior high school students was 23:18, and senior high school students was 0:06 [11]. An additional study from 2005 reported the mean bedtime for students in the fifth grade was 22:10, students in the second grade of junior high school was 23:26, and students in the second grade of senior high school had a mean bedtime of 23:50 [12]. Tagaya *et al.* reported an average bedtime of 0:03 from senior high school students in 2000 [13].

In 3-year-old children, the bedtime delay has resulted in a reduction of total daily sleep [8]. Indeed, in accordance with a recent development in later bedtimes, sleep duration of Japanese children has also reduced. Shimada *et al* [14] examined studies of sleep duration of infants, and concluded that sleep duration in the early 1990s decreased from 12.9 hours in 1985 [15] to 10.9 hours. The nocturnal sleep duration of children aged 3-6 years in 2000 (10.10 hours for children attending kindergarten, 9.35 hours for children attending nursery school, and 9.95 hours for children attending neither kindergarten nor nursery school) was reported to be 9-15 minutes less than in 1995 [16]. Among 21273 children aged 0-36 months from 12 different countries (United States, United Kingdom, Australia, New Zealand, Canada, Hong Kong, Korea, Taiwan, Thailand, Indonesia, Japan, China), Japanese children exhibited the shortest sleep duration (nap + nocturnal sleep duration) of 11.6 hours, while those in New Zealand revealed the longest duration of 13.3 hours [17].

Between 1965 and 2000, the sleep duration of elementary school, as well as junior and senior high school students, in Japan decreased on average by 1.1-1.6 minutes per year [18]. More specifically, mean nocturnal sleep duration in 2004 was 8.77 hours for elementary school students in fifth and sixth grade, 7.42 hours for junior high school students, and 6.55 hours for senior high school students [11]. Similarly, in 2005, mean nocturnal sleep duration was 8.40 hours for fifth-grade elementary school students, 7.23 hours for second-grade junior high school students, and 6.51 hours for second-grade senior high school students [12]. Tagaya *et al.* reported average sleep duration of senior high school students in 2000 to be 6.30 hours [13].

2-2. Complaints of young people with nocturnal lifestyle

In 1979, 8.1% of children attending day nursery schools in Japan were reported to frequently yawn in the morning, and 10.5% were easily tired. By 2000, these numbers had increased remarkably to 53.2% and 76.6%, respectively [19]. Accordingly, approximately 80% of kindergarten and nursery school teachers reported that many children were sleep-deprived [20].

In 2004 in Tokyo, 50% of fifth- and sixth-grade elementary school boys, 60% of fifth- and sixth-grade elementary school girls, 70% of junior high school boys, and 80% of junior high school girls reportedly complained of sleepiness during the third and fourth lesson periods (from approximately 10:00 to 12:00) [21]. In contrast to the early morning (around 4:00) and afternoon (around 14:00) periods, late morning is the period when humans generally tend to be most alert and active [22].

In addition, 47.3%, 60.8%, and 68.3% of fifth-grade elementary school students, second-grade junior high school students, and second-grade senior high school students reportedly experienced sleep deficiency, respectively [12]. The reasons given for sleep deficiency indicated by these students are shown in Table 1.

Table 1: Causes of sleep deficiency [12]

	Elementary school students	Junior high school students	Senior high school students
1	Difficulties falling asleep (43.8%)	TV and video (44.5%)	Cellular phone use (42.4%)
2	TV and video (39.3%)	Homework (32.2%)	TV and video (38.8%)
3	Homework (26.3%)	Difficulties falling asleep (31.1%)	Difficulties falling asleep (27.1%)

The number in parentheses indicates the percentage of students who listed the issue among students who felt they suffered from sleep insufficiency.

A nationwide study to ascertain the prevalence of insomnia, the symptoms, and associated factors among students in junior and senior high schools in Japan revealed a prevalence of difficulty in initiating sleep (14.8%), difficulty maintaining sleep (11.3%), and early morning awakening (5.5%) [23]. The prevalence of insomnia, defined as the presence of one or more of these three symptoms, was 23.5%.

Taking these facts together, young people in Japan are likely to suffer from both daytime sleepiness and nocturnal insomnia. In Japan, it was reported that sleep insufficiency was the main cause of daytime sleepiness in junior high school students, and that inappropriate sleep habits, such as low physical activity level and television viewing, were the potential responsible factors [24]. Exercise is important for good sleep hygiene [25], and an association between the duration of television viewing and irregularity of sleep habits in young children has been described [26]. Television viewing during childhood and adolescence has been associated with increased weight, poor fitness, smoking, and increased cholesterol in adulthood [27]. Watching television, along with playing videogames for an extended period of time, were significantly associated with prolonged sleep onset latency, as well as poor sleep hygiene and an insufficient amount of sleep [28]. Lack of sleep increases body weight [29]. Overweight individuals tend to be less physically active, and reduced physical activity, in turn, exacerbates weight gain. Reduced physical activity and excessive media exposure are likely to be factors that increase inadequate sleep hygiene, which can result in insomnia leading to sleep deficiency and daytime sleepiness.

In addition, the lack of discipline in the home and in public education system, as well as shopping centers that are open 24 hours per day and mobile phone, might contribute to poor sleep hygiene. Data obtained from 17,465 university students, aged 17 to 30 years, that were taking non-health-related courses at 27 different universities in 24 countries, revealed that both male and female students in Japan exhibited the shortest sleep duration and the highest rate of self-rated unhealthiness [30]. In addition, according to the study performed by Walt Disney Studio Home Entertainment in 2008, sleep duration of individuals aged 18-64 years was shortest in Japan, from the 17 countries evaluated [31]. I wonder that most adults, including parents in Japan, do not view sleep as a valuable behavior and, therefore, neglect sleep, which might lead to increased prevalence of inadequate sleep hygiene among the younger generation.

The major complaints of elementary school and junior high school students in 2001 in Tokyo [10] are listed in Table 2. Most of these complaints were consistent with symptoms described as associated features of behaviorally induced deficient sleep syndrome (irritability, concentration and attention deficits, reduced vigilance, distractibility, reduced motivation, anergia, dysphoria, fatigue, restlessness, lack of coordination, and malaise) in the International Classification of Sleep Disorders-2 (ICSD-2) [32]. Can these complaints, however, be explained by sleep insufficiency?

As mentioned previously, bedtime delay in youngsters reduces total daily sleep duration [8], and approximately 80% of kindergarten and nursery school teachers reported that many children are

Table 2 Major complaints of students (>20%) [10]

Elementary school students
persistent need to yawn (62%), desire to sleep (58%), desire to lie down (47%),
eyestrain (33%), difficulties to sit straight (29%), memorizing difficulties (28%), irritated (27%),
neck stiffness (26%), low activity (25%), difficulties to concentrate (25%),
hypersensitive (24%), thirsty (21%), make many mistakes (20%)
Junior high school students
desire to sleep (boys/girls: 73.8%/80.8%), persistent need to yawn 43.6%/69.1%),
desire to lie down (43.2%/47.2%), eyestrain (40.7%/44.7%),
memorizing difficulties (35.2%/33.6%), neck stiffness (29.3%/35.1%),
lumbago (26.5%/23.2%), low activity (21.3%/28.0%),
hypersensitive (20.0%/27.0%), difficulties to concentrate (21.0%/23.8%),
irritated (20.5%/24.2%).

sleep- deprived [20]. In fact, sleep deprivation has been demonstrated to exert a negative effect on daytime functions [33-35], general well being [36], metabolic and endocrine function [37, 38], and body weight [29]. However, the required sleep duration of an individual person is very difficult to determine, because the need for sleep is variable and depends on several factors [39]. Adults normally sleep for varied lengths of times, and such habits are considered to develop at a young age [32]. Of course, these differences should not mean that one should not take care of their sleep duration. If individuals are alert and active during late morning, then they are more likely to have healthier sleep duration, sleep quality, and life rhythms.

3. Nocturnal lifestyles and behaviors

Not only a shortage of sleep duration, but also delayed bedtimes and wake-up times are known to produce physical, mental, and/or emotional problems.

3-1. Adults and older children

Later bedtimes and wake-up times are significantly associated with sub-clinical manic-type symptoms among working adults [40], and evening-type medical school students are reported to experience reduced sleep efficiency compared with morning-type students [41]. To determine if an individual is a morning-type or evening-type person, a self-assessment questionnaire was used. According to an original report [42], morning-type people went to bed and arose significantly earlier than evening-type people. Evening-type young adolescents in Taiwan exhibited a greater association with mood and anxiety symptoms [43]. Among 6631 adolescents aged 14.1-18.6 years, evening-types were found to exhibit more attention problems, perform more poorly in school, experience more injuries, and were emotionally upset more often than the other chronotype individuals [44]. Japanese junior high school students, with an evening preference, were reported to be more likely to exhibit poorer sleep-wake parameters and lifestyle habits than those with a morning preference [45], and there was a greater association between evening-type individuals and impulsivity in students [46]. Compared with morning-type students, evening-type 12- to 13-year old students were reported to be more likely to exhibit behavioral/emotional problems, suicidal behavior and ideation, and habitual substance use [47]. Evening-type children aged 8-13 years have been shown to exhibit a greater tendency towards antisocial behavior, rule-breaking, attention problems, conduct disorder symptoms in boys, and aggression towards others in girls [48].

According to a nationwide survey, students in Japan with regular bedtimes and waking times showed better school performance than those with irregular sleeping times [49]. And conversely, an irregular lifestyle is known to be associated with delayed bedtimes and waking times. Of the college students surveyed, those with poor sleep quality exhibited less regularity in social rhythms relative to those with good sleep quality, and later rising times and bedtimes were reported to be associated with worse sleep quality [50]. Moreover, in adult populations, evening-type people are reported to demonstrate a more irregular daily lifestyle than morning-type people [51].

These reports all suggest an association between delayed waking times, bedtimes and irregular lifestyle with problematic behaviors of older children, adolescents, and adults.

3-2. Studies on preschoolers

Although few studies have described an association between sleep habits and behavior in preschoolers, problematic behaviors among children aged 4 to 6 years have been associated with late and irregular waking times and bedtimes, but not with sleep duration [52].

Suzuki *et al.* [53] compared the relationship between a 2-week sleep diary and the ability to copy a triangular figure on the first attempt in 222 children aged 5 and 6 years. The children who successfully copied the triangle had significantly earlier mean morning wake-up times, as well as significantly longer mean total sleep duration, compared with children who failed to copy the triangle. Compared with children with regular sleep-wakefulness rhythms, children with irregular sleep-wakefulness rhythms exhibited a 5.9-times greater risk of inability to copy the triangle. A semi-structured interview with 16 teachers identified 48 troublesome episodes in 42 children. The rate of children with irregular sleep-wakefulness rhythms among the children with the troublesome episodes (19/42) was significantly greater than children without troublesome episodes (15/180).

These results suggested that children with irregular sleep-wakefulness rhythms exhibit more behavioral problems, as well as problems with integration of cognitive and motor activity.

In a separate study, 204 children, aged 12-40 months (mean 22.6 months), were assessed for daily average physical activity counts per minute (PA) [54]. Results showed that increased age, male gender, and early wake-up times exhibited significant positive correlations with PA.

4. Nocturnal lifestyle and neurological systems

The above-mentioned studies on preschoolers, along with previously cited papers on older children, adolescents, and adults, report problematic behaviors that are associated with delayed wake-up times, delayed bedtimes, and an irregular lifestyle. Although delayed bedtimes also resulted in sleep loss [8], problematic behaviors were found to be more likely associated with delayed wake-up times, delayed bedtimes, and an irregular lifestyle, regardless of sleep duration [52]. In the following section, the presumed neuronal mechanisms associated with these results will be addressed.

4-1. Biological clock

Circadian signals are relayed from the SCN to the hypothalamic dorsomedial nucleus via the subparaventricular zone. The dorsomedial nucleus of the hypothalamus combines inputs from the SCN with inputs from other areas, allowing for flexible control, and sends signals to structures that regulate various circadian rhythms, such as feeding, locomotion, sleep-wake alternation, corticosterone secretion [55], and the autonomic nervous system [56]. Typically, the endogenous period of the circadian clock is longer than 24 hours, and it is through exposure to sunlight in the morning people become accustomed to the 24-hour cycle [57]. Conversely, light exposure at night delays the circadian clock phase [57], or disrupts its function [58-60]. Non-photic cues, such as eating times [61] and activity [62], also serve to synchronize the circadian system to a 24-hour day. In the absence of time cues, daily rhythms become altered, developing their own rhythm. After spending life under such conditions for a considerable period of time, the staging of various biological rhythms changes, such as sleep-wakefulness and temperature [63]. Under such conditions, reciprocal phase interactions within circadian rhythms are disturbed. In general, most people spontaneously awake in the morning when the body temperature begins to rise from its lowest level and, conversely, fall asleep at night when the body temperature begins to decline from its highest level. However, once this reciprocal interaction is impaired, the phase relationship between body temperature and sleep-wake circadian rhythms is disrupted [63], known as circadian desynchronization [64, 65]. This condition might produce various physical and mood disturbances (disturbed nighttime sleep, impaired daytime alertness and performance, disorientation, gastrointestinal problems, loss of appetite, inappropriate timing of defecation, excessive need to urinate during the night). Similar complaints and mood alterations have been observed in patients with jet lag [66], seasonal affective disorder [67], and in astronauts [68].

Endogenous phasing of the circadian biological clock in morning-type individuals varies from evening-type individuals [69], who experience a temperature rise later in the morning and later waking times [70]. Moreover, individuals who are alert in the morning experience an earlier circadian rhythm temperature peak than do individuals who are alert in the evening [71]. These reports suggested that evening-type individuals suffer from circadian desynchronization [64, 65]. Those with delayed waking times and bedtimes, and an irregular lifestyle (an evening preference) are hypothesized to suffer from circadian desynchronization.

Arendt *et al.* [66] showed that jet lag recovery rate, which is attributed in large part to temporary circadian desynchronization, varies with individuals, as well as with the direction of time zone change. The susceptibility for developing symptoms, presumably due to desynchronization, is likely to vary in different individuals. In this regard, the following reports suggest that desynchronization susceptibility is affected by biological background.

Nilssen *et al.* [72] compared the prevalence of sleep disorders in two ethnically different populations living in the same extreme arctic climate. More than 50% of the Norwegian population in these studies [72, 73] resided in the northern region of Norway, whereas the Russian subjects were primarily recruited from the southern part of Russia and the Ukraine. The study determined that Russians exhibited a greater prevalence of sleep disorders than Norwegians. A one-year prevalence of self-reported depression was also compared in the two populations [73], with similar results. The authors [72, 73] postulated that insufficient acclimatization after migration to the north resulted in these effects. Susceptibility to these symptoms was presumably due to desynchronization, which was likely affected in part by unknown biological background factors, including acclimatization. However, acclimatization cannot be altered within one generation.

4-2. Melatonergic system

Melatonin not only regulates the circadian phase [74], but also acts as a hypnotic, is an effective free-radical scavenger and antioxidant, and directly induces gonadotropin-inhibitory hormone expression [75]. Interestingly, bright light during nighttime decreases melatonin secretion [76].

The existence of immunoreactivity against melatonin was demonstrated in the bacterium *Rhodospirillum rubrum*, one of the oldest species of living organisms, at possibly 2-3.5 billion years [77]. Bacterial melatonin might provide on-site protection of bacterial DNA against free-radical attack. Melatonin is also known to exert antioxidant effects in the brain [78], and sleep is hypothesized to function as an antioxidant or scavenging process in the brain [79].

Melatonin promotes and synchronizes sleep by acting on SCN-expressing melatonin MT1 and MT2 receptors, respectively. Synthesized melatonin receptor agonists exhibiting increased duration of action are expected to provide significant clinical value for treating insomnia patients [80]. The onset of melatonin secretion begins 14-16 hours after waking, usually around dusk [81]. Exposure to bright, midday light has been shown to increase melatonin secretion during the night, without a circadian phase shift [82]. Although the results are preliminary, in a study of 3-year-old children, early sleepers tended to exhibit higher levels of urinary 6-sulfatoxymelatonin (6SM) (6SM/creatinine ratio), the primary melatonin metabolite, compared with late sleepers [83].

Decreased melatonin levels in aged zebrafish have been shown to correlate with altered circadian rhythms [84]. Danel *et al.* observed an inversion in melatonin circadian rhythm secretion in alcoholics, not only during intake, but also during short- and long-term withdrawal. They concluded that circadian disorganization of melatonin secretion could be responsible for desynchronization in some alcoholic patients [85]. Because melatonin regulates the circadian phase [74], altered melatonin secretion could disturb circadian oscillation, producing various biological alterations. Nevertheless, in the rat, altered melatonin rhythm had no effect on circadian rhythms of locomotor activity and body temperature [86].

4-3. Serotonergic system

Exposure to morning sunlight has been demonstrated to activate the serotonergic system [87] and, conversely, a nocturnal lifestyle is unlikely to activate the serotonergic system. Moreover, depression correlates with decreased norepinephrine, serotonin, or both [88]. In addition, selective serotonin reuptake inhibitors, which increase the availability of serotonin at the synaptic cleft, have been widely used to treat depression. Emotional instability, typical in indivi- duals with nocturnal lifestyles, might be associated with insufficient serotonergic activity. The seroto- nergic system is activated through rhythmic move- ments, such as gait, chewing, and respiration [89]. Adequate physical activity could, therefore, be important for the activation of serotonin. Exercise- derived benefits for brain function have been demonstrated at the molecular level [90], and physical activity has been reported to decrease the risk of Alzheimer's disease [91–94]. Physical activity, which activates serotonergic activity, is one of the key factors in promoting brain function in animals and humans.

The concept of low serotonin syndrome, which comprises aggressiveness, impulsivity, and suicidal behavior- has been proposed [95]. In adult, male, vervet monkeys, decreased serotonergic activity was reported to be a disadvantage, and enhanced activity an advantage, for attaining high social dominance status [96]. Disturbance in the lateral orbito-prefrontal circuit induces aggressive behavior and loss of sociability [97], and the serotonergic system has been shown to activate this circuit [98]. Serotonin levels, which are increased through exercise, have been shown to enhance learning ability [91]. Serotonergic activity is profoundly affected by the sleep-wakefulness cycle, exhibiting highest activity while waking, and lowest activity during rapid eye movement sleep [99]. Taking these facts together, it has been postulated that irregular sleep-wakefulness rhythm disturbs emotional control and sociability, due to decreased serotonergic activation in the lateral orbito- prefrontal circuit.

It is likely that circadian desynchronization results in unsatisfactory physical, mental and/or emotional conditions, presumably leading to decreased physical activity. If physical activity becomes too low, then the serotonergic system will not be activated. This is further confounded by a lack of morning light. The following negative cycles (solid filled lines in Figure 1) can be postulated in those with delayed wake-up times, delayed bedtimes, and an irregular lifestyle.

4-4. Reported disease conditions associated with circadian disruption

Miike *et al.* [100] described altered circadian rhythms in childhood chronic fatigue syndrome, and reported that these patients suffered from an atypical, but continuous, jet lag condition. A British cohort study over more than 30 years [101] revealed that sedentary behavior during childhood increased the risk of chronic fatigue syndrome/myalgic encephalomyelitis, for which depression is a major symptom. Selective serotonin reuptake inhibitors have been reported to be effective in treating chronic fatigue syndrome patients [102]. It has been assumed that decreased serotonergic activity is involved in the occurrence of this syndrome. Melatonin has also been shown to be effective for chronic fatigue syndrome patients with delayed circadian rhythm [103]. One third of children with chronic fatigue syndrome exhibited abnormal cardiovascular regulation during postural changes (orthostatic dysregulation), which is characterized by instantaneous orthostatic hypotension, postural, or neural-mediated syncope [104]. Orthostatic dysregulation is a well-established clinical concept among pediatricians in Japan.

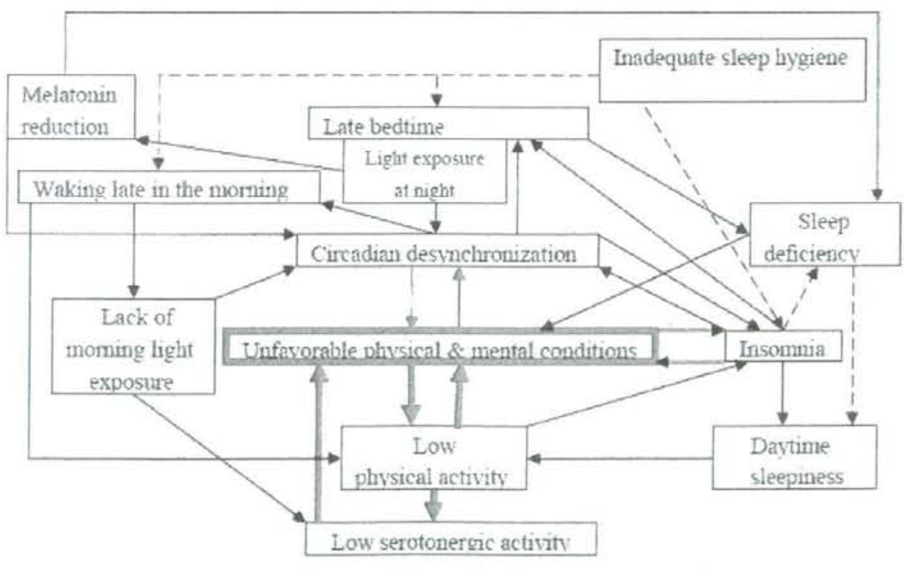

Figure 1 Schematic drawing of the development of asynchronization modified from Fig. 1 in reference 4.

The characteristic clinical burnout symptoms, first described in 1974 [105], comprise excessive and persistent fatigue, emotional distress, and cognitive dysfunction. These symptoms are common among disorders such as depression, chronic fatigue syndrome, and vital exhaustion [106]. Burnout is positively associated with poor sleep quality, a sensation of not feeling refreshed upon awakening, and sleepiness and/or fatigue during daytime [107]. Burned-out subjects are reported to exhibit a higher frequency of arousal during sleep [106]. A study of University Hospital nurses revealed that daylight exposure for at least 3 hours per day resulted in reduced stress and greater job satisfaction, both of which were favorable factors for reducing burnout [108]. Because bright, midday light increases melatonin secretion during the night in elderly individuals [82], the melatonergic system, as well as the serotonergic system [109], might be involved in the pathogenesis of burnout.

Appels *et al.* introduced the terminology of vital exhaustion, which is conceptually akin to burnout [110]. In a prospective study of a large sample of healthy men, vital exhaustion was shown to comprise three factors - fatigue, depressive affect, and irritability - and the risk of subsequent myocardial infarction was attributed to fatigue from vital exhaustion [111]. Vital exhaustion is also associated with sleep disturbances. Polysomnographic recordings indicated that deep sleep stages were significantly reduced in exhausted subjects, compared with control subjects, suggesting that normal restoration processes, which occur while sleeping, are impaired in exhausted subjects [112]. In addition, exhausted subjects presented with a greater number of sleep complaints, shorter sleep duration, frequent napping, and poorer sleep quality [110, 113-115].

Fibromyalgia is characterized by widespread pain and muscle tenderness lasting at least three months, as determined by palpation [32]. Patients with fibromyalgia commonly complain of light and non-refreshing sleep, fatigue, cognitive difficulties, and psychological distress, including symptoms of depression and anxiety. Interestingly, a serotonin and norepinephrine-reuptake inhibitor has been reported to be successful in these patients [116], as well as melatonin for treating the pain associated with fibromyalgia [117].

Decreased circadian rhythm amplitude has also been reported in a more common condition - depression [118]. Moreover, decreased amplitude in circadian core body temperature changes was reported in delinquent student patients diagnosed with a desynchronized condition [119]. External and internal desynchronizations were two of the three major components of jet lag [120]. Another major component was sleep deprivation [120]. External desynchronization refers to the conflict between the internal clock and external time cues. As an individual is exposed to new, external, time cues, the internal clock adjusts to the new time zone, which may take several days. Internal desynchronization, a loss of phase coupling between phenolmena revealing circadian oscillation, takes place during readjustment of internal clocks, and each system adjusts itself differently. Internal desynchronization can also be induced by acute manipulation resulting in phase alteration [121], which is the case in jet lag. As a result of internal and external desynchronization, sleep loss occurs, which decreases the quality and quantity of various activities [29, 33-38]. This ultimately results in decreased serotonergic activity. For the trans-meridian traveler, both physical cues such as daylight and darkness, and social cues, such as mealtimes and noise, encourage realignment of the circadian system.

In contrast, for the shift worker, physical cues are resolutely opposed to nocturnal alignment, as are most social cues stemming from a day-oriented society. Therefore, circadian realignment of shift workers takes longer than realignment from jet lag [122]. In addition, a forced, extraordinary schedule can also induce desynchronization [123]. As previously mentioned, alcoholics have been reported to display an inversion of melatonin circadian rhythm secretion, which could be respon- sible for their desynchronization [85].

As described in this review, chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, depression, jet lag, and shift work are likely to be a result of desynchronization and decreased serotonergic, as well as decreased melatonergic activity, although each of these disease conditions possesses its own specific origin, major symptoms, and course. There is a similar pathophysiology between these disease conditions and the condition that many Japanese preschoolers/students are currently suffering from.

5. Asynchronization

More than half of the preschoolers/students in Japan complained of daytime sleepiness, while about one quarter of junior high school students in Japan suffer from insomnia. Moreover, as shown in Table 2, frequent complaints of students in Japan were compatible with associated features of behavioral-induced sleep-deficient syndrome [32], most likely due to inadequate sleep hygiene. If this were the case, these symptoms should be ameliorated following adequate sleep (by exclusion of dotted lines in Figure 1). However, such therapeutic approaches often fail. The students cannot fall asleep, despite sleep loss, and this is partly due to inadequate sleep hygiene consistent with excessive media exposure and low-level physical activity. Indeed, delayed wake-up times and bedtimes could be symptoms of a delayed sleep phase form of circadian rhythm sleep disorder. Although this article does not discuss this disorder in detail, it should be noted that there is confusion between this disorder and the biological- and lifestyle-related sleep phase delays that are especially common during adolescence [124]. It is possible that certain factors other than simple sleep loss and inadequate sleep hygiene are involved in many of the young people in Japan that exhibit delayed wake-up times, delayed bedtimes, and an irregular lifestyle. It has been assumed that decreased activity in the melatonergic and serotonergic systems, as well as desynchronization, are candidates for explaining pathophysiology.

5-1. Presumable pathophysiology

In 1976, Aschoff and Wever described [125] that activity rhythm (wakefulness and sleep) and other rhythmic variables (*e.g.*, temperature) often have similar circadian periods of approximately 25 hours. However, on occasions, the activity period may become substantially longer (*e.g.*, 33 hours), while other rhythms continue with a period of about 25 hours. Such a state is termed internal desynchronization. Thus circadian desynchronization is used to indicate a loss of phase coupling between certain phenomena, which lead to circadian oscillation. It should be noted that this term arose from basic studies, and was not originally a clinical-related term.

Individuals with delayed wake-up times, delayed bedtimes, and an irregular lifestyle may also exhibit a loss of phase coupling between phenomena, circadian oscillation, and decreased amplitudes of other phenomena, although no concrete evidence has obtained to date. Desynchronization alone is not adequate to describe the clinical conditions that many young people in Japan are suffering from. In addition, many of these individuals likely display reduced serotonergic and/or melatonergic activity. I wonder a novel, clinical entity is required to improve understanding of the pathophysiology of these disturbances [3, 4].

In 1970, Winfree [5] reported that a specific, dim, blue-light, pulse stimulus, with a unique stimulus time and duration, resulted in unusual broadening of the daily eclosion peaks of the fruitfly, *Drosophila pseudoobscura*, even to the extreme of obscuring circadian rhythm. This phenomenon was termed "circadian singularity behavior", and has been described in a range of organisms, such as algae, plants, and mammals [126-131]. In humans, Jewett *et al.* [128] reported circadian rhythms of rectal temperature and plasma cortisol were abolished by a single, long duration, bright-light pulse administered during one or two successive circadian cycles. Huang *et al.* [132] demonstrated that temperature increases and light pulses can trigger singularity behavior in Neurospora circadian clock gene frequency. In addition, Ukai *et al.* [58] reported that a critical light pulse (3-hour light pulses delivered at a specific circadian time (CT) ~17 (near subjective midnight (=CT18))) drives cellular clocks to singularity behavior in mammals. Interestingly, this phenomenon is transient [132], although removal of the stimulus is needed.

Taken together with this basic entity – singularity -, I designed a novel clinical concept –asynchronizatiopn-. Asynchronization is the result of disturbed aspects (*e.g.*, cycle, amplitude, phase, and interrelationship) of biological rhythms that normally exhibit circadian oscillation, which presumably involves decreased serotonergic and/or melatonergic activity. The major trigger of asynchronization is hypothesized to be a combination of light exposure during nighttime, which reduces melatonin secretion, and a lack of morning light exposure, which decreases serotonergic activity. Thus asynchronization symptoms (Table 3) include disturbances of the autonomic nervous system (sleepiness, insomnia, disturbed hormonal excretion, gastrointestinal problems, sympathetic nervous system predominance, *etc.*), as well as higher brain functions (disorientation, loss of sociability, loss of will or motivation, impaired alertness and performance, *etc.*). Neurological (attention deficits, aggression, impulsiveness, hyperactivity, *etc.*), psychiatric (depressive disorders, personality disorders, anxiety disorders, *etc.*) and somatic (tiredness, fatigue, neck and/or back stiffness, headache, *etc.*) disturbances are also putative symptoms of asynchronization. Complaints introduced in this article (Table 2) could be symptoms of asynchronization.

To detect the disturbance of biological rhythms, actigraphic recordings [133], as well as diurnal measurements of body temperature, corticosteroids, and melatonin are useful. Takimoto *et al.* monitored human clock genes in whole blood cells to evaluate internal synchronization [134]. The early phase of asynchronization is hypothesized to be functional and can be relatively easily resolved by establishing a regular sleep-wakefulness cycle. However, without adequate intervention, disturbances can gradually worsen, resulting in decreased serotonergic and/or melatonergic activity, which can be difficult to resolve. In Figure 1, red lines, especially the broad ones, are hypothesized to be involved in asynchronization. A portion of patients with chronic fatigue syndrome, orthostatic dysregulation, burnout, vital exhaustion, fibromyalgia, and depression are thought to suffer from asynchronization.

5-2.Potential therapeutic approaches

5-2-1. Basic principles

For synchronization of the biological clock to a 24-hour cycle, morning light and avoidance of nocturnal light are essential. Therefore, avoidance of these two behaviors will result in asynchronization. Moreover, light-induced adrenal gene expression and corticosterone release have been demonstrated [135]. Under normal conditions, steroid secretion is greatest in the morning.

Table 3: Asynchronization

Essence	Disturbance of various aspects (*e.g.*, cycle, amplitude, phase, and interrelationship) of biological rhythms that indicate circadian oscillation.
Presumable causes	Light exposure during the night. Lack of light exposure in the morning Decreased physical activities. Disturbance of the biological clock and/or the serotonergic system.
Symptoms	Disturbances related to the Autonomic Nervous System sleepiness, insomnia, disturbance of hormonal excretion, gastrointestinal problems, sympathetic nervous system predominance Somatic Disturbances tiredness, fatigue, neck and/or back stiffness, headache, persistent yawn, desire for sleep, wish to lie down, inactivity, lumbago Disturbances related to Higher Brain Function disorientation, loss of socility, loss of will or motivation impaired alertness and performance, difficulties to remember, difficulties to concentrate Neurological Disturbances attention deficit, aggression, impulsiveness, hyperactivity, irritated, hypersensitive Psychiatric Disturbances Symptoms observed in depressive disorders, personality disorders, and anxiety disorders
Therapeutic approaches	Morning light, an avoidance of nocturnal light exposure, conventional approaches - light therapy, medications (hypnotics, antidepressants, melatonin, vitamin B12), physical activation, chronotherapy and alternative ones - Kampo, pulse therapy, direct contact, control of the autonomic nervous system, respiration (qigong, tanden breathing), chewing, crawling
Prognosis	Early phase: Disturbances are functional and can be relatively easily resolved, *e.g.*, through establishment of a regular sleep-wake cycle Chronic phase: Without adequate intervention, disturbances can gradually worsen involving loss of serotonergic activity, which is difficult to resolve

In addition to light and social factors [123], food [136] is known to affect the circadian clock. The dorsomedial hypothalamic nucleus was determined to be a putative food-entrainable circadian pacemaker in mice, and oscillation of this pacemaker was found to persist for at least 2 days, even when mice received no food during the expected feeding period following establishment of food-entrained behavioral rhythms [61]. Regular mealtimes, as well as participation in social activities, are likely to prevent asynchronization.

A daytime nap is known to result in favorable performance [137]. However, evening-type adolescents were reported to nap more frequently during school days than other chronotypes [44], although improved school performance after an afternoon 15-minute-nap was reported in a Japanese high school [138]. Further studies are needed to determine whether napping affects asynchronization.

Nevertheless, to prevent asynchronization, the social promotion of favorable sleep hygiene is important [139, 140].

5-2-2. Conventional approaches

5-2-2-1. Light therapy

Light therapy has been shown to effectively treat patients with depression [141, 142] and seasonal affective disorder [143]. It has been recommended that patients with seasonal affective disorder initially receive morning light shortly upon awakening [67]. In patients with winter depression (seasonal affective disorder), one week of bright, morning light (2500 lux) treatment produced significantly greater remission rates (53%) than evening (38%) or midday (32%) treatment [144]. A clinical trial [67] that administered 5 weeks of bright, morning light therapy (10000 lux, 60 minutes) to chronic (≥ 2 years) major depression out-patients resulted in a remission rate of 50%, while the control group showed only minor improvements. Light therapy also reduced depress- sion scores in patients with fibromyalgia [145].

The effects of light therapy on chronic fatigue syndrome have, however, been controversial [146, 147]. As described previously, exposure to at least 3 hours daylight per day was suggested to produce favorable effects on burnout patients [108], and light therapy was used to treat patients with shift work and jet lag disorders [148]. However, in animals and humans, short nights attenuate both evening light-induced circadian phase delays and morning light-induced circadian phase advances [149, 150]. In addition, circadian clocks advance phases by inducing earlier waking time and bedtime, while circadian clocks delay phases by pushing waking and bedtime later [151, 152]. Although these light effects should be clues for treating patients with early phase asynchronization, attenuation of light-induced circadian phase delays during short nights results in decreased light therapy effects on individuals suffering from jet lag and night workers engaged in a nocturnal life with a long nocturnal photoperiod (= short nights) [150].

5-2-2-2. Medications

5-2-2-2-1. Hypnotics

There is insufficient evidence to assess the safety and efficacy of hypnotic medication for delayed sleep phase disorder [153]. Data encompassing the safety and efficacy of hypnotics with other types of circadian rhythm sleep disorders are scant [153]. In addition, the effects of hypnotics on shift work disorder patients are inconsistent [148]. However, the use of hypnotics for jet lag-induced insomnia is a rational treatment and is consistent with standard recommendations for treating short-term insomnia. The efficacy of benzodiazepines on patients with fibromyalgia, together with non-steroidal anti-inflammatory drugs, has been inferior to amitriptyline [154]. In addition, ultra-short- or medium-acting hypnotics have been used in children with chronic fatigue syndrome [147], and are widely used to treat insomnia in depression patients [155]. It is likely that appropriate use of hypnotics should be taken into consideration for the management of asynchronization.

5-2-2-2-2. Antidepressants

The efficacy of antidepressants has been reported in depression, as well as chronic fatigue syndrome [102] and fibromyalgia [116, 154]. These agents could also be promising for treating depressive tendencies in asynchronization patients. However, because asynchronization involves serotonin depletion, the use of selective serotonin reuptake inhibitors or serotonin and norepinephrine-reuptake inhibitors should not be used as the first agent of choice for treating asynchronization.

5-2-2-2-3. Melatonin and its agonists

The effects of melatonin in patients with delayed sleep phase disorder and free-running disorder have been established [153]. Afternoon or evening melatonin administration would be expected to shift rhythms earlier, thereby correcting pathological phase delay. Appropriately timed melatonin administration has been shown to entrain totally blind individuals with free-running disorder. Melatonin or melatonin agonists might benefit daytime sleep in night workers through their hypnotic, as well as phase-shifting, effects [148]. Melatonin, administered at the appropriate time, can reduce symptoms of jet lag and improve sleep following travel across multiple time zones [148]. Melatonin is also effective treatment for some patients with chronic fatigue syndrome [103], as well as pain associated with fibromyalgia [117]. Interestingly, agomelatine, a compound with melatonin receptor agonist properties, has been reported to exert an antidepressant effect superior to selective serotonin reuptake inhibitors and selective serotonin and noradrenaline reuptake inhibitors [156]. However, because melatonin is not regulated by the U.S. FDA, there are a variety of preparations, and its usefulness has been limited [157].

In a 4-year-old boy diagnosed with Smith-Magenis syndrome, Carpizo *et al.* reported treatment with a beta (1)-adrenergic antagonist in the morning (to suppress diurnal melatonin secretion) and melatonin in the evening (to generate nocturnal melatonin peak), which resulted in improved sleep quality, as evaluated by polysomnographic methods [158]. This approach could be beneficial for asynchronization patients that exhibit altered diurnal melatonin secretion.

5-2-2-2-4. Vitamin B12

Vitamin B12 has been shown to enhance light pulse-induced phase shifts and thus augment entrainability of the circadian clock to light in rats [159]. In fact, high-dose vitamin B12 (3 g/day) proved to be effective in childhood chronic fatigue syndrome patients with free-running disorder [147]. An association between low vitamin B12 status and depression in elderly individuals has been suggested [160]. Because vitamin B12 deficiency causes decreased remethylation of homocysteine and is, therefore, most likely contributing to increased homocysteine levels, Regland *et al.* [161] measured homocysteine and vitamin B12 levels in cerebrospinal fluid of patients that fulfilled criteria for both fibromyalgia and chronic fatigue syndrome. They measured increased homocysteine concentrations, as well as a correlation between vitamin B12 levels and clinical variables. In other words, decreased vitamin B12 levels resulted in more severe clinical conditions. However, a recent review suggested that vitamin B12 was not an effective treatment for delayed sleep phase disorder [153]. Also, vitamin B12 was not recommended for treating jet lag or shift work disorders [148].

5-2-2-3. Physical activity

Physical activity is associated with an antidepressant effect in clinical depression [162]. Exercise leads to improved physical and mental health in fibromyalgia patients [163] and was shown to re-time circadian rhythm in individuals suffering from jet lag or shift work [164]. In patients with chronic fatigue syndrome, graded exercise therapy was shown to be valuable in randomized controlled trials [165]. Exercise induces these effects not only through the serotonergic systems, which is activated by rhythmic movements, such as gait, chewing, and respiration [89], but also through other molecules, such as brain-derived neurotrophic factor [90]. Physical activity or exercise could be potentially used to relieve asynchronization. Each morning in Japan, we have a 10-minute radio program of gymnastic exercises with piano accompaniment. This set of exercises is very familiar to almost all people in Japan, especially those older than twenty years of age. The efficacy of these exercises should be re-evaluated for physical and mental health.

5-2-2-4. Chronotherapy

To resynchronize the circadian clock with the desired 24-hour cycle, chronotherapy has been used in patients with circadian rhythm sleep disorder. This approach assumes that the circadian clock cycle of the majority of people is longer than 24 hours. In a case of delayed sleep phase, a successive delay of sleep onset by 3 hours each day, over a 5-6-day period, is required to achieve desired sleep onset [166]. This shift should be rigidly adhered to establish a set sleep-wake schedule and proper sleep hygiene practice. However, the potential confounding effects of light exposure at inappropriate circadian times might limit the effectiveness and practicality of this approach [167].

5-2-3. Alternative approaches

The following are potential approaches to manage asynchronization, although the diagnostic standards and methodology, in terms of applicability, remain to be determined.

5-2-3-1. Kampo

Kampo medicine is a traditional Japanese herbal medicine that originated from traditional Chinese medicine. Examples for prescription are listed in Table 4 [168-170]. In addition to these prescriptions, Kanbaku-taisou-to (72) and Yoku-kan-san (54) is the author's preference for patients with early-phase asynchronization and presumed elevated sympathetic nerve activity (the value in parentheses is the standardized number for prescription in Japan). I also use Dai-saiko-to (8) to treat insomnia due to hypertension or tinnitus. In patients with depression [171] and fibromyalgia [172], Kampo or traditional Chinese medicine have been commonly used.

Table 4 Presumable Kampo prescriptions for asynchronization

		weakness (in the lower extremities)	systemic hypofunction and/or coldness	glowing (or heat sensation in the palm or foot)	apathy	aggressiveness or impulsiveness	depressive tendency	anemic	GI disturbance	fatigue after acute infection
fatigue syndrome	Rokumi-gan (87), Hochu-ekki-to (41) and Sho-Saiko-to (9) [168]									
chronic fatigue syndrome	Ninjin-yoei-to (108) [168] [169]	Hachimi-jiou-gan (7) [170]	Shinbu-to (30) or Ougikenchu-to (98) and Ninjin-to (32) [170]	Rokumi-gan (87) [170]				Zyuzen-taiho-to (48) and/or Ninjin-yoei-to (108) [170]	or insomnia Kihi-to (65) or fatigue Hochu-ekki-to (41) [170]	Saiko-keishi-to (10) [170]
child patients with school refusal				Rokumi-gan (87) [170]	Seisho-ekki-to (136) [170]	Saiko-karyu-kotsuborei-to (12) [170]	Kami-shouyou-san (24) [170]	Zyuzen-taiho-to (48) and/or Ninjin-yoei-to (108) [170]	or insomnia Kihi-to (65) Hochu-ekki-to (41) [170]	

Number in the parenthesis is the standardized number for prescription in Japan

5-2-3-2. Rhythmic movements

As described in the former section, exercise could produce favorable effects on depression [162], fibromyalgia [163] jet lag, shift work [164], and chronic fatigue syndrome [165], presumably not only through the activation of serotonergic system [89] but also by the induction of other molecules [90]. Among rhythmic movements which activate serotonergic system [89], gait must be a part of exercise. In this section, rhythmic movements other than gait –respiration and chewing- will be introduced.

Qigong is an ancient, oriental, mindful exercise [173], also described as a mind-body, integrative exercise or traditional Chinese medicine intervention that is used to prevent and cure ailments, as well as to improve health and energy levels [174]. Qigong (or ch'i kung) refers to a wide variety of traditional "cultivation" practices that involve movement and/or regulated breathing [175]. Qigong has recently been designated as an alternative therapy to help meet the increasing demand of non-pharmacologic modalities for achieving bio-psycho-social health in patients suffering from anxiety [173] or pain [176]. Although the meta-analyses to date have been based on low-quality studies and small numbers of hypertensive participants, Qigong and Zen meditation have been shown to significantly reduce blood pressure [177].

Tanden breathing involves slow breathing (range of 0.05-0.15 Hz) into the lower abdomen, and was found to affect cardiac variability, which is controlled by the autonomic nervous system [178]. Although rhythmic respiration has been reported to activate serotonergic activity [89], Arita and Takahashi [179] preliminarily determined that tanden respiration also elevates serotonergic activity. Chewing has also been reported to activate the serotonergic system [89, 180]. This behavior could be used to manage asynchronization by deliberately activating serotonergic activity.

Locomotion is a sort of rhythmic movements. Failed locomotion (crawling) during infancy (lack of interlimb coordination between upper and lower extremities) has been reported to be due to hypofunctioning serotonergic and/or noradrenergic neurons [181]. This results in postural atonia by disfacilitating postural augmentation pathways and/or disinhibiting the postural suppression path- way and preventing locomotion [182]. Forced-crawl training has been described as relieving symptoms resulting from low serotonergic activity [183].

5-2-3-3. Direct contact

An older generation Japanese pediatrician [184] was quoted to say, "Holding a baby in the arms ("dakko" in Japanese) is the most effective tranquilizer for a baby." Although therapeutic touch is now receiving attention as a method to manage anxiety disorders, including depression [185]. dakko is a typical and classic daily behavior that involves direct contact between caretakers and youngsters. With the rapid spread of various types of media, including mobile phones, one concern is that direct contact between people is rapidly diminishing. In fact, concurrent television exposure is reported to correlate with fewer social skills [186]. In addition, hugging and intimate, face-to-face conversations are expected to be promising in the effort to manage and/or prevent asynchronization.

5-2-3-4. Control of the autonomic nervous system

To provide adequate cues for the circadian clock, morning activation of the sympathetic nervous system and evening stimulation of the parasympathetic system might be helpful to manage asynchronization. In Japan, some pediatricians recommend scrubbing the skin with a dry towel or cold water in the morning to train the autonomic nervous system in patients with orthostatic dysregulation [187]. However, this approach has not been covered in the recently published guideline [188].

5-2-3-5. Pulse light

In addition to the removal of stimuli that induce singularity effects, adequate stimuli (light pulse at CT 9-15 (transition from subjective day to night) [58]) could also reverse singularity. Further studies are needed to identify adequate stimuli for reversing circadian singularity behavior in asynchronization.

6. Conclusion

Many young people in Japan suffer from daytime sleepiness and nocturnal insomnia, and are persistently tired and inactive. This review focused on the association between nocturnal lifestyle and biological clock disorders, as well as the melatonergic and serotonergic systems. However, involvement of dopamine [189] and opioid peptides [100] are also possible. A novel clinical concept - asynchronization - has been proposed, and a similar basic concept - singularity - was also introduced.

In this review, studies that recommended morning-type behavior to reduce behavioral/ emotional problems were introduced [28, 47, 52]. Ayurveda, an ancient system of health care that is native to the Indian subcontinent, suggests that, in addition to good conduct, thought, diet, interpersonal dealings, physical activity, early rising, and early bedtimes are good for a healthy life [190]. Ekken Haibara wrote in his essay, Youzyoukun (1713), that one should awake early in the morning and avoid late bedtime to live a healthy life [191]. Byoukesuchi (Hirano, 1832), a book describing medical practices for the home, stated that one should go to bed early at night and awake before dawn for a healthy life [192]. Thus both traditional wisdoms and recent researches recommend morning-type behavior, and this article reviewed the possible background mechanisms for the favorable effects on physical and mental health.

Senior high school students in Korea are reported to go to bed (0:54 on school nights) [193] later than those in Japan (0:06 [11] or 23:50 [12]). Although Chinese senior high school students in Hong Kong went to bed earlier (23:24) than those in Japan, it was concluded that they did not receive sufficient sleep [194]. Many young people not only in Japan but also in the other countries might be potential patients with asynchronization. In addition, some NEET (Not in Employment, Education, or Training) [195] individuals might also suffer from asynchronization.

Now we are living in the society with 24-hour activity. I am afraid that this type of society might produce unfavorable effects on the SCN. A quarter of the world's population is subjected to a 1 hour time change twice a year (daylight saving time; DST) [196]. DST is now known to disturb normal seasonality seen in sleep timing assessed by mid—sleep times [196]. In addition, at the beginning of DST (=spring), the rates of traffic accidents [197] and the attacks of myocardial infarction [198] are reported to increase. I wonder we should be more careful on the property of the biological clock. I hope a novel concept of asynchronization to contribute to noticing the significance of the SCN, and to helping patients suffering from circadian disruptions.

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