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PREFACE

Futures in Sleep Research and Medicine

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In September of 1987, I joined the Stanford Sleep Research Center from the Hayaishi Bioinformation Transfer Project operated at Osaka Medical College, Japan. Since then I have been involved in basic sleep research for over 27 years.

During this period, there have been numerous movements and transformations in sleep research and medicine around the world, and I would like to express my personal view about the future of sleep research and medicine in the preface of this issue of the Sleep and Biological Rhythm.

When I started basic sleep research in the USA, there were many passionate adventures in our research field. We, of course, worked hard day and night and discussed the results and research plans with passion among colleagues. The atmosphere in the field was not excessively competitive, and we had chances to communicate, discuss, and exchange research ideas with other basic and clinical sleep researchers in the world frequently. We became friends and colleagues quickly. The research fund was just enough, and we were able to focus on our research topics of interests. Sleep research had been established as one of the promising and attractive research fields in Neuroscience.

This was good since sleep research attracted many young scholars and students, and every sleep meeting was full of trainees, and some of them decided to devote their life to sleep research.

The mammalian clock gene was cloned in 1994 by J. Takahashi (1), and this quickly lead to the comprehensive understandings of the cellular mechanisms of the circadian clock. The groups form Stanford University and University of Texas Southwestern Medical Center independently discovered the narcolepsy genes in experimental animals in 1999 (2, 3), and this immediately lead to the discovery of the major pathophysiology of human narcolepsy (i.e., orexin/hypocretin ligand deficiency) (4).

These are bright sides of sleep/circadian research history in the last decade of 20th century. Around the same time, the researchers started to worry about the future of the sleep research field, namely lack of research or faculty positions and that of the research fund. Some promising young investigators needed to change their research topics of professions due to these limitations. The research field rapidly became competitive, especially for research funding, and every PI (principle investigator) needed to spend significant amounts of their time writing research grants and for obtaining the research fund.

We, at Stanford, worked like a donkey for about 2 years immediately following the discoveries of the canine narcolepsy gene, as the orexin/hypocretin system was just discovered one year prior, in 1998 (5). Therefore, there were plenty of things to do in order to understand how the orexin/hypocretin deficiency induces narcolepsy and how sleep/wake are regulated by the orexin/hypocretin system. We put our first priority to do actual experiments rather than writing grants or proposals without the grants to specifically support these experiments. This short period was probably the most productive in our research history. Two years later, we could finally take a breath, and we started thinking of writing the grants with full of progresses and new data. However, we were so shocked to be told by government officers that so many grants focused on the orexin/hypocretin system were already awarded in the past 2 years, and it may be difficult for the institute to award additional grants on the same topics.

We however, succeeded to survive and continue the research we wanted to do, but needed to spend more significant amounts of time on grant writing than before.

Together with the rising federal deficits and spending on antiterrorism efforts and the wars in Iraq and Afghanistan, the government budget for research had

been reduced significantly, and the pay line become half or less compared to previous years (less than 10% of grants submitted were awarded) entering into the period of "winter years". The period of tough funding lasted much longer than we initially thought, and this was reflected in changes in the rules for the government grant submissions. The number of revision allowed was reduced from 2 to 1 (3 strike out to 2 strike out, and only a total of 2 submission are allowed) in 2009. Worst of all, if the original grant submission was not funded, the PI was not allowed to submit the grant with the same research aims anymore. This was checked by the grant officers with an aid of a specific computer program, and some PIs needed to give up their life-work with the depressing 2 strike out rule, and some PIs even gave up research/academic career and closed the lab.

I must admit that this harsh situation was not only limited to the sleep research field, but also was true for most other biomedical research. A recent paper by Alberts *et al*., discussed about these systemic flaws in the perspective in PNAS (6). The authors claimed that the long-held but erroneous assumption of never-ending rapid growth in biomedical science has created an unsustainable hypercompetitive system that is discouraging even the most outstanding prospective students from entering our profession—and making it difficult for seasoned investigators to produce their best work. This is a recipe for long-term decline, and the problems cannot be solved with simplistic approaches. The authors proposed the following specific recommendations in the paper, (i) Planning for Predictable and Stable Funding of Science, (ii) Bringing the Biomedical Enterprise into Sustainable Equilibrium, (iii) Grant-Making That Improves Scientific Productivity, and (iv) Addressing Policies That Undermine Sustainability (see details in (6)).

I believe that the recent unsustainable hypercompetitive system also creates imbalances in distribution of the funds and in some cases, misconducts in biomedical research.

As if in response to this, the NIH changed their grant submission rules early this year (http://grants.nih.gov/grants/policy/amendedapps.htm), and the NIH now allows PIs to resubmit the research proposal that was previously not funded. This change may be too late, as many promising researchers already gave up their research careers.

I was pleased to learn that Dr. Yanagisawa recently founded the International Institute for Integrative Sleep Medicine in Tsukuba University with the aid of Japanese government research fund (http://wpi-iiis.tsukuba.ac.jp/). The Institute is supported with a long-term and large research grant, and we can expect steady progress and break through. However, it was very unfortunate that Osaka Bioscience Institute (OBI), City of Osaka and industry funded biomedical research institute, which included the leading sleep research group in the world, was closed due to budget cuts of the City.

Sleep research should be translational and taxpayers should receive merits from the research outcomes, especially for research that is supported by the public agencies. In this aspect, there will be much to do for sleep scientists, and I am pleased to learn these efforts, including advises on shift work, jet lags, and daylight saving were made in Japan by various sleep specialists. Sleep and performance and accidents are highly associated with each other, and this should be emphasized in various environments, occupational health, schools, and athletes.

I am also pleased to know about successful efforts by JSSR and Public Interest Incorporated Foundation for public education for sleep hygiene/problems in Japan (http://www.jfnm.or.jp/nemurin/shiminkouza.html; http://www.c-linkage.co.jp/jssr39/pdf/jssr39_shimin_A4_0422_1.pdf).

As I am a basic sleep researcher, I mostly mentioned about the situation in basic sleep research. However, I must emphasize that importance of sleep hygiene, diagnosis and management of sleep disorders have been re–recognized recently, partially because their causative relationship to incidence of metabolic syndromes and higher mortality rates (7).

The rapid increase in medical cost is one of the major economic concerns in the modern and aging society, and the medical cost for treating sleep disorders is not an exception. Interestingly, however, a study by Albarrak in Canada, nicely demonstrated that for OSAS cases, the treatment of OSAS reversed the trend of increasing health-care utilization seen prior to the OSAS diagnosis (8), suggesting that the OSAS can be a source of many of diseases.

PSG evaluation which costs up to several thousand dollars/per PSG, for example, is still very expensive, labor intensive, and time consuming, and a need for a shift from PSG was proposed in the USA and other countries. I think this is highly possible, as many new sensors and technologies have been developed recently, together with the developments in bioinformatics and in abilities of handling big data.

Non-invasive long-term sleep monitoring at home or at nursery homes will become especially important, in the aging society, as sleep changes occur with physical

and mental diseases and vise versa, and both conditions significantly affect QOL of elderly subjects.

Sleep medicine is multidisciplinary, and we need to collaborate and incorporate many different faculties of medicine, science, institutes of technologies, and we need to work together to gain the understandings in sleep physiology and pathophysiology in health and diseases and to improve QOL of the public.

Considering the scientific expandability, I am sure the sleep research and medicine will be able to have bright future, but nothing will be gained without our efforts.

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