THE RECENT HISTORY OF SEASONAL AFFECTIVE DISORDER (SAD)

The transcript of a Witness Seminar held by the History of Modern Biomedicine Research Group, Queen Mary, University of London, on 10 December 2013

Edited by C Overy and E M Tansey

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WHAT IS A WITNESS SEMINAR?

The Witness Seminar is a specialized form of oral history, where several individuals associated with a particular set of circumstances or events are invited to meet together to discuss, debate, and agree or disagree about their memories. The meeting is recorded, transcribed, and edited for publication.

This format was first devised and used by the Wellcome Trust's History of Twentieth Century Medicine Group in 1993 to address issues associated with the discovery of monoclonal antibodies. We developed this approach after holding a conventional seminar, given by a medical historian, on the discovery of interferon. Many members of the invited audience were scientists or others involved in that work, and the detailed and revealing discussion session afterwards alerted us to the importance of recording 'communal' eyewitness testimonies. We learned that the Institute for Contemporary British History held meetings to examine modern political, diplomatic, and economic history, which they called Witness Seminars, and this seemed a suitable title for us to use also.

The unexpected success of our first Witness Seminar, as assessed by the willingness of the participants to attend, speak frankly, agree and disagree, and also by many requests for its transcript, encouraged us to develop the Witness Seminar model into a full programme, and since then more than 50 meetings have been held and published on a wide array of biomedical topics.[1] These seminars have proved an ideal way to bring together clinicians, scientists, and others interested in contemporary medical history to share their memories. We are not seeking a consensus, but are providing the opportunity to hear an array of voices, many little known, of individuals who were 'there at the time' and thus able to question, ratify, or disagree with others' accounts – a form of open peer-review. The material records of the meeting also create archival sources for present and future use.

The History of Twentieth Century Medicine Group became a part of the Wellcome Trust's Centre for the History of Medicine at UCL in October 2000 and remained so until September 2010. It has been part of the School of History, Queen Mary, University of London, since October 2010, as the History of Modern Biomedicine Research Group, which the Wellcome Trust

[1] See pages 109–114 for a full list of Witness Seminars held, details of the published volumes and other related publications.

funds principally under a Strategic Award entitled 'The Makers of Modern Biomedicine'. The Witness Seminar format continues to be a major part of that programme, although now the subjects are largely focused on areas of strategic importance to the Wellcome Trust, including the neurosciences, clinical genetics, and medical technology.[2]

Once an appropriate topic has been agreed, usually after discussion with a specialist adviser, suitable participants are identified and invited. As the organization of the Seminar progresses and the participants' list is compiled, a flexible outline plan for the meeting is devised, with assistance from the meeting's designated chairman/moderator. Each participant is sent an attendance list and a copy of this programme before the meeting. Seminars last for about four hours; occasionally full-day meetings have been held. After each meeting the raw transcript is sent to every participant, each of whom is asked to check his or her own contribution and to provide brief biographical details for an appendix. The editors incorporate participants' minor corrections and turn the transcript into readable text, with footnotes, appendices, a glossary, and a bibliography. Extensive research and liaison with the participants is conducted to produce the final script, which is then sent to every contributor for approval and to assign copyright to the Wellcome Trust. Copies of the original, and edited, transcripts and additional correspondence generated by the editorial process are all deposited with the records of each meeting in the Wellcome Library, London (archival reference GC/253) and are available for study.

For all our volumes, we hope that, even if the precise details of the more technical sections are not clear to the non-specialist, the sense and significance of the events will be understandable to all readers. Our aim is that the volumes inform those with a general interest in the history of modern medicine and medical science; provide historians with new insights, fresh material for study, and further themes for research; and emphasize to the participants that their own working lives are of proper and necessary concern to historians.

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[2] See our group's website at www.histmodbiomed.org.

ACKNOWLEDGEMENTS

The topic of 'Seasonal Affective Disorder' came about as a possible subject for a collaborative Witness Seminar with the Centre for the History of Emotions and we are very grateful to Dr Thomas Dixon, Director of the Centre, for his help in the planning of this meeting. We thank Professor Sir Brian Follett for his excellent chairing of the occasion and Professor Philip Cowen for writing the introduction to the volume. Our gratitude also goes to the Wellcome Library, London, for permission to use photographs from the meeting and the Guilford Press for permission to reproduce documents from *Winter Blues*; also to Ms Carol Barksfield and Professor Josephine Arendt for providing images for the volume and the archives.

As with all our meetings, we depend a great deal on Wellcome Trust staff to ensure their smooth running: the Audiovisual Department, Catering, Reception, Security, and Wellcome Images. We are also grateful to Mr Akio Morishima for the design and production of this volume; the indexer Ms Liza Furnival; Mrs Sarah Beanland and Ms Fiona Plowman for proof reading; Mrs Deborah Gee for transcribing the seminar; Ms Emma Jones for assisting with running the seminar and Mr Adam Wilkinson who assisted in the organization and running of the meeting. Finally, we thank the Wellcome Trust for supporting this programme.

Tilli Tansey

Caroline Overy

School of History, Queen Mary, University of London

ILLUSTRATIONS AND CREDITS*

* Unless otherwise stated, all photographs were taken by Thomas Farnetti or David Sayer, Wellcome Trust, and reproduced courtesy of the Wellcome Library, London.

ABBREVIATIONS

DLMO	Dim light melatonin onset
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
FDA	Food and Drug Administration, USA
ipRGC	Intrinsically photosensitive retinal ganglion cells
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PRC	Phase response curve
RD	Retinal degeneration
SAD	Seasonal affective disorder
SADA	The Seasonal Affective Disorder Association
SCN	Suprachiasmatic nucleus
SPAQ	Seasonal pattern assessment questionnaire
SSRI	Selective serotonin reuptake inhibitor
TSH	Thyroid-stimulating hormone

INTRODUCTION

Psychiatric diagnosis is controversial and is regarded by some principally as a means of reinforcing the vested interests of medical professionals and pharmaceutical companies. On the other hand, the phenomena that are described in clinical psychiatric practice are real and clearly extend across time and between cultures. 'In every culture there is some notion of emotional or psychological difference. Not all cultures identify these differences in the same way, nor do they use identical terms. Equally, however no culture is indifferent to those who are sad, frightened or unintelligible in their conduct.'[1]

The description and diagnosis of Seasonal Affective Disorder (SAD) or 'winter depression' is a comparatively recent development which provides an unrivalled opportunity to explore the construction of a psychopathological entity through the relevant peer-reviewed publications, as well as the professional and public reaction to these scientific discoveries. This Witness Seminar provides a riveting insight into the thinking of some key protagonists, both the scientists who developed the diagnosis of SAD as well as those for whom this new clinical entity resonated so clearly with their own experiences.

What is the point of diagnosis? Ideally a diagnosis should point to a particular disease process, though even in general medicine this is often not the case. However, in a pragmatic sense the value of diagnosis is that it enables a group of people manifesting particular clinical phenomena to be identified as sharing a common prognosis and response to treatment – in the case of SAD a therapeutic response to artificial bright light. Indeed with SAD, it may be that increasing knowledge about the circadian effects of bright light stimulated a search for medical conditions in which it might be effective, that is, in some sense the availability of a treatment led to the identification of the condition.

How truly recent is the identification of SAD as a diagnostic entity? In fact, seasonal variation in mood disorder has long been recognized and Rosenthal and colleagues (1984) quote the eminent nineteenth-century psychiatrist, Emil Kraepelin, as commenting in his standard textbook: 'Repeatedly I saw in these cases moodiness set in in autumn and pass over in spring … corresponding in a certain sense to the emotional changes which come over even healthy individuals at the changes of the season...'[2]

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[1] Rogers and Pilgrim (2010), page 26.

[2] Kraepelin, cited in Rosenthal *et al.* (1984), page 76.

Kraepelin here is talking about bipolar disorder and raises some critical issues that are still relevant to the nosological status of SAD. Thus, is SAD really a form of bipolar disorder or does it make more sense to regard it as an exaggeration of a 'normal' seasonal mood change that might affect most of us to some degree? Original descriptions of SAD found that the majority of patients could be indeed diagnosed with bipolar disorder (winter depression, followed by mania or hypomania in the summer) but in subsequent samples, unipolar depression has predominated.[3] Whether or not there are reliable seasonal changes in mood in the general population still seems uncertain, but if there are such changes, patients with mood disorders may be more sensitive to them.[4]

In current diagnostic frameworks such as *DSM-V*, SAD is regarded primarily as a mood disorder (recurrent major depression or bipolar disorder) with a characteristic seasonal manifestation, where the seasonal pattern is referred to as a 'specifier'. However, Rosenthal (2009) has argued that SAD should be considered a separate diagnostic entity both from the point of view of a specific response to bright light treatment, a distinct 'atypical' depression symptom profile (over-eating, over-sleeping, afternoon slump in energy), and a particular pathophysiology involving abnormal melatonin secretion and altered physiological responses to light.[5]

Nevertheless, while bright light treatment is effective in the treatment of SAD, it is apparently also beneficial in non-seasonal depression and overall the number of patients studied in randomized trials is small; moreover, establishing a plausible placebo control has been problematic.[6] Clinically, it does seem to be the case that SAD patients with the characteristic 'atypical' depressive symptom profile do best with bright light treatment,[7] though atypical depressive symptoms are also seen in other depressive conditions, including bipolar disorder. Does bright light primarily treat the SAD disorder or rather, the atypical symptoms (which are not, of course, syndrome specific)? Finally, the nature of the pathophysiological abnormality in SAD is still not firmly established; Lewy's hypothesis[8] that SAD patients have abnormally delayed circadian rhythms that are corrected by morning bright light is compelling and elegant but not yet confirmed in a large sample of patients.

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[3] Rosenthal *et al.* (1984); Thompson and Isaacs (1988).

[4] Winthorst *et al.* (2014).

[5] Rosenthal (2009).

[6] Simon (2005).

[7] Stinson and Thompson (1990).

[8] Lewy *et al.* (2007).

This Witness Seminar is particularly topical in view of the recent intense interest in the role of circadian rhythm and sleep physiology in a variety of mental health problems. This has been stimulated, in part, by fundamental research on 'clock' mechanisms in animals and the role of clock genes and their associated regulatory pathways in the circadian regulation of neural networks.[9] These advances promise greatly to enrich SAD research and should eventually help us decide whether SAD is much like other kinds of mood disorder or rather, is best considered as a distinct entity.

This seminar is made particularly compelling by the testimony of some of the outstanding scientists and clinicians whose work led to the development of the concept of SAD. The studies of Josephine Arendt were fundamental in demonstrating the role of melatonin in the organization of seasonal and circadian rhythms, while Al Lewy's groundbreaking discovery that melatonin secretion in humans could, in fact, be modulated by particularly bright artificial light laid the foundation for the modern light treatment of a range of circadian disorders. Norman Rosenthal used his own experience of the psychological effects of New York winters compared to those of his native South Africa to develop the clinical concept of winter depression and communicate this understanding to receptive patients and the public. Not then, a story of scientific progress through the crunching of 'big data' but more an account of how ingenuity, flair and a rather spontaneous coming together of the right people led to truly original discoveries and a new treatment for depression that has been appreciated by so many.

Professor Philip Cowen
Professor of Psychopharmacology
University of Oxford

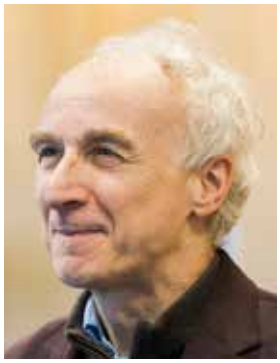

Figure A: Professor Philip Cowen

[9] Foster and Kreitzman (2014).

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THE RECENT HISTORY OF SEASONAL AFFECTIVE DISORDER (SAD)

Participants*

Professor Josephine Arendt
Ms Carol Barksfield
Professor Ilana Crome
Dr Thomas Dixon
Ms Jennifer Eastwood
Professor Sir Brian Follett (Chair)
Ms Helen Hanson
Professor Alfred Lewy
Professor Gerald Lincoln
Professor Rob Lucas
Professor Norman Rosenthal
Professor Tilli Tansey

Also present: Professor Peter Crome

Apologies include: Dr Melanie Abas, Professor Anthony Cleare, Professor John Eagles, Professor Russell Foster, Dr Michael Hastings, Professor Andrew Loudon, Professor Declan Murphy

* Biographical notes on the participants are located at the end of the volume

Professor Tilli Tansey: Thank you very much for coming here to the Wellcome Trust for our Witness Seminar on SAD. I'm Tilli Tansey and I'm the convenor of the History of Modern Biomedicine Group, which is based at Queen Mary University of London (QMUL).[1] This format of Witness Seminars was devised in the mid-1990s as a way of recording and stimulating interest in the recent history of biomedicine and we invite a group of people, who have been involved in particular discoveries or changes or debates, to tell us what really happened. We want to get the stories behind the published, formal literature. We want to learn what stimulated particular fields or retarded discoveries, what were the unexpected successes and what were the failures and why? All of these conversations are recorded, transcribed, edited, and published. We produce hard copies and everything is also made freely available on our website. These are planned as informal meetings so we want everyone to contribute as and when you wish. Nothing will be published without your permission, and we will ask you to assign copyright to the Wellcome Trust.

The subject of SAD came about as a result of a discussion between me and my colleague, Thomas Dixon, who is the director of the Centre for the History of Emotions at QMUL, and we thought it would be a very suitable far-ranging subject for discussion to have what we hope is the first of many collaborations. Thomas, do you wish to say a few words?

Dr Thomas Dixon: As Tilli just said I run the Centre for the History of the Emotions, the only such research centre, you might not be particularly surprised to hear, in the UK.[2] One of our main areas of interest in the five years that we've existed is the relationship between the history of emotions and the history of medicine, emotions in health, and emotions in disease. When Tilli and I spoke, this seemed like a really excellent topic for investigating the recent history of emotions and health, as Seasonal Affective Disorder, or SAD, is one of those relatively rare conditions[3] that's come into common parlance – people who are not experts in the field make reference to it, describe, and experience their own emotional lives through this medical label of SAD. It's something that's got into popular culture. So for our purposes that makes it really interesting to look at the way that language has changed, experience has changed, and emotions change, all as part of the history of modern biomedicine. That's probably

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1 See www.histmodbiomed.org

2 See the History of the Emotions website at www.qmul.ac.uk/emotions/index.html (visited 4 June 2014).

3 See later comments on page 31.

enough to indicate why I think it's really interesting, and how it fits with our work at the Centre.

Tansey: The point of these meetings is not to hear from historians like Thomas and me but to hear from you, the authentic voices. What really went on? You've all been involved in different ways at different stages in the recent history of SAD. So to aid these discussions we've drawn up a brief outline programme (Table 1) and we hope that our discussions will broadly follow this format, but please feel free to contribute whenever and as often as you wish.

What is SAD?
How, when, where, and why did it first appear? Relationship to views on 'feeling low in winter'?
Who was/became involved (e.g. scientists, clinicians, patient groups, and funding agencies), when and how?
What is the evidence for SAD and has it changed over time? How widespread has SAD become?
What have been the views of the psychiatric profession and other practitioners?
The theories of causation
What has been thought to be its physiological basis?
How and when did the concept arise of it being linked in some manner to our internal clocks (circadian or seasonal)?
What other physiological bases/explanations have been offered for SAD (unrelated to internal clocks but perhaps related to effects of season)
Diagnosis and therapy
Diagnosis of SAD, how has it changed?
The development of specific therapies – failures and successes; commercial interests
Patient activism
How have therapies been thought to work?
What status have these therapies had in terms of clinical diagnosis, psychiatric practice, health insurance industry, etc?

Table 1: Outline Programme for 'The Recent History of Seasonal Affective Disorder (SAD)' Witness Seminar

Figure 1: Professor Tilli Tansey and Professor Sir Brian Follett

An important component of all of these meetings, of course, is to find a suitable chairman. Sir Brian Follett is an endocrinologist who has spent much of his career studying biological cycles in animals and especially how many of these are controlled by changes in photoperiod. He has also served as Biological Secretary of the Royal Society, the chairman of the Arts and Humanities Research Council, and as Vice Chancellor of Warwick University. So he brings much relevant knowledge and experience to the role of today's chairman, and Brian, we're incredibly grateful to you for agreeing to take on this task and accept this invitation.

Professor Sir Brian Follett: We're here this afternoon not to produce *the* history of SAD but *a* history of SAD, so it won't be a complete picture – indeed, there are ghosts in the room who are not here. I know rather little about the topic, and it is not an area I've ever worked on. But I have picked up a few thoughts: SAD was first recognized in the early 1980s[4] but ever since there has been controversy as to whether SAD is a discrete condition and significantly more than a depressive state that happens to coincide with certain times of the year. The latest evidence is that SAD may be a real depressive condition that is seasonally triggered. It seems that we have to consider it to be a 'complex

[4] Seasonal Affective Disorder was first described in 1984 (Rosenthal *et al.* (1984)). For a longer history, see Rosenthal (2006), pages 264–74; Wehr and Rosenthal (1989).

Figure 2: Professor Josephine Arendt

disorder with genes, environment and culture contributing to its etiology',[5] but that sentence worries me because that is the way so many ill-defined medical conditions are explained away. So what we'd like to do is to trace a history and establish what are the 'facts' and what is 'opinion'. Let us begin and spend some time thinking about what is SAD? Then I'd like to turn to what its underlying physiological causation may be. That edges us into clocks and all sorts of things that are affected by day length. Finally, we will consider diagnosis and therapy.

Professor Josephine Arendt: First of all I'm most honoured to be here. I'm not a psychiatrist but I have some very good psychiatrist friends and I'd like to say immediately that Norm (Norman Rosenthal) and Al (Alfred Lewy) advised me in 1984 on how to use light treatment for possible SAD in the Antarctic winter. I have photographs of this occasion.[6]

The year 1984 really was the start of enormous interest in this whole area, which began, I think, because the time was right. We knew from the biologists and other scientists studying photoperiodism, for example our chairman, and

[5] Whitehead (2004).

[6] Professor Josephine Arendt wrote: 'I had just been asked by the British Antarctic Survey to give the base doctor at Halley (75°S) a research project to keep him busy. I have photographs of this occasion which happened during a Gordon Conference.' Note on draft transcript, 29 January 2014. The photos were not of sufficient resolution to publish in this volume but copies are deposited with the records of this meeting in Archives and Manuscripts, Wellcome Library, London at GC/253.

Gerald Lincoln, my own group, and others, that day length governed seasonal responses in animals.[7] We knew that the day length signal was pineal melatonin[8] and that its duration of secretion – long in short days and short in long days[9] – told animal physiology how long the night (or day) was.[10] We knew, thanks to Al, how much light it took to suppress melatonin completely[11] and therefore in theory it was possible to devise a treatment of summer day length (i.e. shorten melatonin secretion with light) for a winter season of depression. Norm's famous paper in 1984[12] and preceding case reports were the start of all of this.[13] I will obviously not go into any more detail on that because particularly Norm and Al will have an enormous amount to say.

There has been much discussion as to the mechanism and there are lots of theories around. My Antarctic interest proved to be a bit of a flop because we and others could find little SAD in Antarctica, just low mood and not in the winter, more in the spring.[14] But giving a skeleton light treatment (a one hour bright light pulse in the morning and another hour in the early evening) without change in mood did produce a wonderful shift in circadian phase during the Antarctic winter.[15] And I think that probably relates to some of the theories as to how light treatment works.

I won't go into drugs at all but I'm sure lots of other people will. I'm really sorry that neither Chris Thompson nor Stuart Checkley[16] are here because our other involvement was the ability to measure melatonin and its urinary

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7 Lincoln and Short (1980).

8 Herbert, Stacey and Thorpe (1978); Hoffmann (1979).

9 Arendt (1979); Illnerová, Hoffmann and Vaněcek (1984).

10 Carter and Goldman (1983a and b); Yellon *et al.* (1985); Arendt (1986); Goldman (2001).

11 Lewy *et al.* (1980).

12 Rosenthal *et al.* (1984).

13 Lewy *et al.* (1982); Rosenthal *et al.* (1983).

14 Palinkas, Houseal and Rosenthal (1996); Harris *et al.* (2010).

15 Professor Josephine Arendt added: '[This was] one of the first studies to show a light pulse phase shift in humans. See Broadway, Arendt and Folkard (1987).' Note on draft transcript, 29 January 2014.

16 Professor Chris Thompson is a practising psychiatrist and has been Chief Medical Officer of Priory Group since 2004; Professor Stuart Checkley is a retired consultant psychiatrist at the Maudsley Hospital, London and Emeritus Professor of Psychoneuroendocrinology. For further biographical details see the notes on pages 80 and 86. Both Professor Thompson and Professor Checkley were invited to the Seminar but did not attend.

Figure 3: Professor Norman Rosenthal

metabolite 6-sulphatoxymelatonin[17] both for NIMH (Norman Rosenthal and Tom Wehr) and for the Maudsley (Chris Thompson and Stuart Checkley).[18] We helped them hopefully track what was happening in their SAD projects and I'm delighted to have been associated with these groups.[19] Another person it would have been very nice to see would have been Tom Wehr (NIMH) but he doesn't come to things very much these days I believe.[20]

Follett: Thank you, Jo, for getting us started. Would you like to say something, Norman?

Professor Norman Rosenthal: First I'd like to thank everybody for this lovely event and thank Jo for, as always, being so concise in encapsulating some of the key issues. I know that at this point you're looking for what we in the United

[17] Arendt, Paunier and Sizonenko (1975); Arendt *et al.* (1985b).

[18] Thompson *et al.* (1988); Winton *et al.* (1989); Checkley *et al.* (1993); Murphy *et al.* (1993).

[19] Professor Josephine Arendt wrote: 'We also collaborated with Anna Wirz-Justice at the University Psychiatric Clinic in Basel (for example, Wirz-Justice *et al.* (1996)) who has been very important in this field in Europe. She and Michael Terman (Columbia, NY) have been active raising the profile of light treatment and with Francesco Benedetti have recently published a clinician's manual for the field (Wirz-Justice, Benedetti and Terman (2009)).' Note on draft transcript, 29 January 2014.

[20] Dr Thomas Wehr is Scientist Emeritus at the National Institute of Mental Health and a psychiatrist in private practice in Bethesda, MD. See page 86 for further biographical information.

States call the backstory. So here are a few details from my own perspective. I came to the United States from South Africa in 1976 with my wife and little child and encountered experiences that I had never had before, namely when the days became short and dark I personally experienced a draining away of energy and a difficulty getting all my tasks accomplished for the three winters that I was in New York City. This turned around in the spring and I got my energy back, and each time I would think: 'What the heck is going on here? What's this all about?' I never had had it before in South Africa, where Johannesburg is 26 degrees south, whereas New York is 40 degrees north. I didn't put all the pieces together, but as the snow would melt I would think: 'Oh, my energy's coming back with the melting of the snow, what was that fuss all about these last three months? You can do everything, why were you exaggerating the difficulties?' My wife had it much worse than me, she was virtually bed-ridden for some of that time. And so somewhere internally, something was getting encoded in me. Now at the time when I was studying psychiatry, the only thing I heard of was the 'Christmas Crunch'. Patients would say to me: 'Do you know, everybody in the office has the "Christmas Crunch" and they're all having difficulties' and that's all that I heard about it. Winter depression was never taught in any way in my studies. I was going to do research at the NIH, I had the good fortune to be at a party where I met Al Lewy, who was dating a woman who was in our residency, and he talked to me about his melatonin study and I thought it was absolutely fascinating. He was working for a group that included Tom Wehr and was involved in rhythms of light and mood, not light so much then, the light was really the suppression of melatonin but was involved in circadian rhythms.[21] So rhythms and mood and light were all kind of converging, and here I would like to agree with Jo that in a way the time was right, that there were a lot of converging lines. In due course I went to the NIH and joined that group, maybe Al was, in part, actually instrumental in helping get me into that group. Anyway, we started there and at that point an engineer named Herb Kern contacted us. He had kept diary records of his moods for many years and had hypothesized that they were seasonal and being driven by light. He came our way and wanted to be treated and Tom Wehr was very interested in sleep deprivation. I remember a pivotal discussion between Al and Tom and me, where Al said: 'Let's give him more light', and Tom said: 'This is a perfect person to study sleep deprivation on.' Tom was senior to Al and me, so he outranked us both and he could have ruled on it. I then chipped in and said: 'Look, you can sleep deprive any depressed person but how often do you get somebody with this unique seasonal pattern? I think it would be a real

[21] See pages 12–15.

waste and a shame not to try this highly novel treatment.' And we did and he did actually come out of the depression and that's all been written up in two separate case histories – one by Al, one by myself.[22] Then it occurred to me that we needed more people with this problem. I solicited the opinions of local psychiatrists, none of whom had ever seen the problem, which really proves that if you don't know what you're looking for, you're not going to see it. And they didn't know what they were looking for but I figured, let's go straight to the general public because people like me, had I seen an article in the newspaper, would have seen myself in that article. So a very lovely reporter from the *Washington Post* put in an article in which she described yet another patient who had this, who had been referred to us by a private psychiatrist named Dr Peter Mueller, who was also beginning to think there might be a group of people who are seasonally depressed.[23] She was referred to us, she had a more typical pattern as it turns out than did Herb Kern, and we can elaborate later, but she was the sort of prototypical case vignette that we had, that this journalist put in her article. Thousands of people responded from all over the country. [24] That then became the basis for the syndrome or description and the basis for the first cohort of people to go into that first single blind study, the controlled study that was the subject of the 1984 paper to which Jo was referring.[25]

Follett: Might I ask if this syndrome was widespread in Northern European society, but had not really been reported upon? Looking back, when was it detected in Scandinavia?

Rosenthal: Actually in Scandinavia it was recognized in the culture, because in the northern part of Sweden there's a condition called *lappsjuka*, which means the sickness of the Lapps, which is essentially SAD. In the folk literature of Iceland they have a term called *skamdegistunglindi*, which means the depression of the short days. So it's there in the cultural writings, if not in medical literature. In the medical literature a clear case first emerges by Esquirol in France of a businessman, who came to him at the beginning of the winter and said that in the last several winters he had had a depression that had come on very clearly. He was very concerned because it had influenced his judgement adversely and he was worried that he would do bad things, including violence to his family,

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[22] Lewy *et al.* (1982); Rosenthal *et al.* (1983).

[23] Dr Peter Sterling Mueller (1930–2013) was Clinical Professor of Psychiatry at the College of Medicine and Dentistry of New Jersey. See page 16.

[24] For a more detailed account see Rosenthal (2013), pages 14–15.

[25] Rosenthal *et al.* (1984).

if he were not somehow treated. Esquirol took the seasonal pattern seriously and made the inference that the seasons were somehow driving these recurrent winter depressions and told him that he had to go down to the south of France and from there to Italy in anticipation of the winter, to pre-empt the subsequent depression.[26] In fact the man did so and he successfully treated the depression. Subsequently, in the mid-1940s, there was a description of a patient called an 'unmarried clerk' by a Colonel Frumkes. This man had this depression in the winter every year and Colonel Frumkes was heavily influenced by psychoanalysis so we have very complex descriptions and explanations for why apparently at the beginning of the winter he suddenly realised that masturbation was not a unique behaviour that he had only himself engaged in, but that in fact it was quite common practice, and apparently this at the beginning of the winter had plunged him into regular depressions. In addition, he was very disappointed in Mother Earth, who had let him down by all the trees losing their leaves and everything. So psychoanalytic explanations were offered to explain. So you've got this tremendous disjunction between the excellent clinical objective descriptions of the man's depressions and what strike us today as very outrageous explanations for what is, after all, a rather simple, biological phenomenon.[27] Incidentally, the history of SAD is documented in *Winter Blues* and *Seasonal Affective Disorders & Phototherapy*.[28] And the history of SAD that I've reported to you, that's in *Winter Blues*, was actually contemporaneously verified by all professionals concerned. I had each and every person who was involved in it, Al, Tom, Peter Mueller, Herb Kern, all basically sign off on it contemporaneously and say: 'Yes, this is right', because I didn't want it to subsequently be regarded as my own subjective opinion. I modified and fixed it where anybody had any disagreements.

Follett: Al, is the 'winter blues' common in human societies and does it appear more strongly as one moves away from the equator and annual day lengths alter? In the history of SAD there appears to be a moment when it went from being, as it were, something one lived with, a few people suffered, to becoming a pathological condition that might be amenable to treatment.

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[26] Jean-Etienne Esquirol (1772–1840) was a French psychiatrist who published his two-volume, *Des Maladies Mentales* in 1838. For a discussion see Rosenthal (2006), pages 268–9.

[27] This case was published in the *Psychoanalytic Quarterly* in 1946 (Frumkes (1946)).

[28] Rosenthal (2006), pages 264–74; Rosenthal and Blehar (eds) (1989) pages 14–16. Professor Alfred Lewy added: 'Regarding Norm's account of the early history of SAD research, I would recommend a few other readings to fill in some of the details – Kern and Lewy (1990) and Battacharjee (2007).' Note on draft transcript, 14 February 2014.

Figure 4: Professor Alfred Lewy

Professor Alfred Lewy: First of all, thank you for inviting me to this great event. In my opinion, the key reason why we succeeded in 'discovering' SAD when it was more or less at least anecdotally reported to exist is that we simultaneously began to test a successful treatment, a treatment which was assumed to be related to its underlying mechanism; and, indeed, bright light remains the treatment of choice for SAD. Doctors don't like feeling helpless and for them to feel really interested in a disorder they need to have a treatment. So SAD and light treatment came along almost at the same time: they came along in the case report of Herb Kern.[29] There are many other parts of this story that we can get into, but I thought I might describe some of the early work I did at the NIMH with Tom Wehr and Fred Goodwin that led up to the time when Norm came to the NIMH and joined us when we went on to do the SAD work. I didn't know anything about biological rhythms or melatonin or the pineal gland before I went to the NIMH in 1975 and I joined the research group that Fred Goodwin headed.[30] When I was the most junior person of this team, I went to Tom (this was in mid-1976) and I said: 'I'd like to make a contribution to the chronobiology work.' It was circadian rhythm work at that point, not seasonal. 'And I'd like to develop a technique for measuring melatonin in humans.' So I went off into the lab for a couple of years, mentored by a brilliant organic chemist, Sanford Markey, who taught me gas

[29] Lewy *et al.* (1982).

[30] Professor Frederick Goodwin (b. 1936) is Clinical Professor of Psychiatry at George Washington University. He joined the National Institute of Mental Health in 1965 where he was Director from 1992 to 1994. See further biographical details on pages 82–3.

chromatography-mass spectrometry.[31] We succeeded in measuring melatonin in a very accurate and precise way. To get a little bit personal about this, I remember the day in the lab, it was a weekend or an evening and there was nobody else around, and I realised then that the assay was going to work. You know you cannot publish a failed assay. You can barely publish negative results of a well-done experiment; but a failed measurement technique, nobody is interested in it. But this assay got into *Science* in 1978.[32] But before we sent our paper off, when I realised that the assay was going to work, I remember that moment when I was alone in the lab, calling my father up and telling him that I feel like I'm just putting the finishing touches on a rocket ship that can take me into outer space into unknown territory and it's going to help me discover something – but I don't know what it is yet. Now I have the tool to learn about melatonin in humans and how this may lead to something else. So my father said: 'Well, let's celebrate. Your godfather' – my father's best friend whom he met in World War II – 'has just been named the Governor-General of Australia and I'd like to go visit him. Why don't you come with me and we'll see what the vice-regal life is all about?' So we went to Australia for two weeks and when I returned to Washington DC I thought: 'Well, maybe we could measure my own melatonin in the morning and see how it decreases over successive days from night-time to daytime levels as my body clock readjusts to the East Coast Time Zone.' I didn't have a clue about non-visual, ocularly-mediated light being able to affect humans; all the scientific papers suggested that humans were unique, and they did not suppress melatonin in response to light. Some very distinguished scientists were speculating that humans lacked the retinohypothalamic tract present in other non-human primates, such that they had the light suppression of melatonin capability but humans did not.[33] So I didn't have an inkling about light suppression of melatonin at that point. I just wanted to test the daily rate at which my body clock adjusted through the time zones I crossed following my return from Sydney. I figured that just one (morning) sampling time point would initially show high melatonin levels, which would gradually decrease as my body clock adjusted to the DC time zone.[34] To my

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[31] Dr Sanford P Markey joined the NIMH in 1974 and is head of the Laboratory of Neurotoxicology of the Intramural Research Program.

[32] Lewy and Markey (1978). Professor Alfred Lewy added: 'It remains the gold standard in the field, having directly validated (for example, Fraser *et al.* (1983)), and indirectly established the benchmark for all of the subsequent radioimmunoassays used to the present day.' Note on draft transcript, 14 February 2014.

[33] Perlow *et al.* (1980).

[34] Lewy (1983b).

surprise, the levels were low the first day and I thought: 'Maybe sunlight is suppressing my melatonin levels?' The difference between ordinary room light that previous investigators used and sunlight could be intensity, or it also could be the spectral differences, but in our simplistic way of thinking we just thought maybe it was intensity. So Tom Wehr and I first did a preliminary study of two individuals, who we had sleep between 3 in the morning and 11 in the morning for a week. Then we measured their melatonin profiles and then again on the eighth morning when we opened the windows and let the sunlight stream in at 7am, we saw that the sunlight suppressed their melatonin. We never formally published this finding, which led us to do the following study with Fred Goodwin, David Newsome, and S P Markey.[35] David was the ophthalmologist I asked to help because we were concerned about light toxicities.[36] We were going to use very bright light in the eye, and most people then would not know what we now know is fairly safe if you use the right kind of light. Sandy Markey was my collaborator and mentor for the assay, and I wanted him to be a part of this research team as well. So we took six individuals and we used 2,500 lux, which is about five times brighter than ordinary room light, which is at its brightest around 500 lux; the 2,500 lux light suppressed their melatonin production. We exposed these normal volunteers between 2 and 4 in the morning and then we took just two of them and gave them 1,500 lux and they had a halfway suppression. With just two people in one of the treatment groups, we went out on a limb and said: 'There's a dose-response curve here, or more appropriately, fluence-response curve: the brighter the light, the greater the suppression.' And in that paper we said that bright light, including sunlight, might have effects on biological rhythms in humans as well. I would posit here, and people might want to comment one way or another, that that paper caused a paradigm shift in the field, having had numerous implications that we're still trying to figure out the meaning of all of them.[37] One of the implications was that if humans use electric light or indoor

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[35] Lewy *et al.* (1980).

[36] Dr David Newsome (1942–2011) was head of the Retinal and Ocular Connective Tissue Disease Section of the National Eye Institute at the National Institutes of Health.

[37] Lewy *et al.* (1980). Professor Alfred Lewy wrote: 'This study was the first demonstration of any light suppression of melatonin in humans.' Note on draft transcript, 14 February 2014. Professor Josephine Arendt added: 'There was however already some evidence for light control of circadian rhythms (Orth and Island (1969)).' Note on draft transcript, 19 June 2014. Professor Alfred Lewy commented: 'In response to Jo Arendt's reminder about the above reference, which – along with related citations – were duly acknowledged in our original contribution (Lewy *et al.* (1980)), I am also reminded that with the passage of so many years now is a good time to try to arrive at an informed and objective consensus as to which findings were key (and why).' Email to Ms Caroline Overy, 4 July 2014.

light in the winter starting around 5pm to bedtime, it is not sufficiently bright to affect melatonin production or biological rhythms: we still may be responding to the short natural photoperiod (day length) because even on a cloudy, rainy day it's at least 10,000 lux outdoors during almost all of the day. Thus, we could be experiencing a shorter day in the winter versus a longer day in the summer and therefore have a seasonal signal that wasn't being perturbed by our use of usual intensity indoor light. Another implication was that we could have our circadian rhythms cued to light as well but again it would have to be natural daylight, usually in the morning, to reset our 24-hour rhythms every day, because, as we all know, most of us naturally drift a little later each day in the absence of any resetting cue. In other words, we need a morning light cue to reset us to precisely 24 hours. One reason why this paper caused a paradigm shift was that the received wisdom was that light did not suppress melatonin in humans and that light did not affect circadian rhythms in humans.[38] The received wisdom then was that social cues were the main synchronizers of human circadian rhythms, that humans had evolved in such a way, that we were so intelligent, that we had risen above control by the light/dark cycle. All that thinking changed with our 1980 *Science* paper. There were some other implications of that paper as well.[39] It was just after we discovered light suppression of melatonin production in humans and were in the process of writing this up when Herb Kern contacted us and told us about his

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[38] Wever (1979).

[39] Professor Alfred Lewy wrote: 'The work done by previous researchers did not use sufficiently intense light, which is why they concluded that humans did not respond to non-visual ocularly-mediated light. To his credit, Lennart Wetterberg was perhaps the first to acknowledge that our demonstration that "strong" bright light could suppress melatonin in humans (Wetterberg (1980); Wetterberg (1981)). [This] was what led him to increase the light intensity in his subsequent studies, for example his first bright light treatment study (Beck-Friis *et al.* (1986)). I should also probably mention here that the first investigator to actually test our suggestion using bright light was Dan Kripke (Kripke (1981)), and, to his credit, Wever was the first to use our work to show successfully that bright light could reset biological rhythms in humans (Wever, Polasek and Wildgruber (1983)), although he did not hold the sleep-wake cycle constant. We were to do that (Lewy, Sack and Singer (1984); Lewy, Sack and Singer (1985)) which according to at least one investigator was important (Czeisler *et al.* (1986)). Another implication of our finding that melatonin production could be suppressed by light in humans was that melatonin should be sampled under dim light, so as not to suppress its production, in order to use endogenous melatonin as a marker for the timing of the body clock. And another implication was that some blind people might have free-running rhythms. Yet another implication was that artificial light could be used to experimentally, and perhaps therapeutically, manipulate circadian rhythms in humans, provided it was of sufficient intensity.' Note on draft transcript, 14 February 2014.

seasonal mood cycle.[40] He had read about the melatonin assay and he wanted me to measure his melatonin rhythm because he was a very bright and knowledgeable guy who had read all about the photoperiodic work and seasonal rhythms in animals and knew that length of day was important as well as the duration of night-time melatonin production in regulating seasonal rhythms, and he wanted me to measure his melatonin profile. I said: 'Well, I've got a better idea, we can do that, but we've just discovered that light can suppress melatonin production in humans, so why don't we try treating your next winter depression with light? Herb wasn't the typical Seasonal Affective Disorder patient.[41] He contacted us when he was hypomanic, of course. He had been to several psychiatrists up and down the east coast of the United States where many famous expert psychiatrists live and work. And, with the exception of Dr Peter Mueller, they were not impressed with his type of mood pattern;[42] and Herb (and Dr Mueller) even had some ideas about light therapy, but not about 'bright' light therapy. So then Norm joins the group, and Norm and Tom Wehr were also co-authors of the case report. I made Herb the second author of that case report.[43] In this case report, we exposed him to a skeleton photoperiod. Animals, and again I'm speaking here with very little authority compared to the experts here like Gerald Lincoln, tell the time of the year because of the time interval between when they first get light in the morning and when they last see it in the evening, and so if you want to change their seasonal rhythms you don't need to give them light all day long, you just give them light a little earlier in the morning and a little later in the late afternoon/evening to extend their photoperiod. I figured 13 hours is a good spring photoperiod, so we gave Herb the light between 6 and 9 in the morning, and 4 and 7 in the afternoon. That would be kind of a skeleton photoperiod. It was 2,000 lux light. The time interval between 6 in the morning and 7 in the evening is 13 hours. And so Norm and I both followed him over a ten-day treatment regimen, and Norm and the nurses gave him some behavioural tests. Herb started to respond after about the third or fourth day, and the response was complete after ten days. That became the first case report of a patient with recurring winter depression treated with bright light. The title of that paper wasn't SAD, it was a

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[40] Kern and Lewy (1990); Battacharjee (2007).

[41] Professor Alfred Lewy clarified: 'He had a circannual mood cycle that did not strictly place his depressions in the same months each year, and he also became hypomanic when he wasn't depressed.' Note on draft transcript, 14 February 2014.

[42] See page 10.

[43] Lewy *et al.* (1982).

manic-depressive with a seasonal cycle. I was first and lead author of this case report. Norm was first and lead author of another case report describing Herb's prior mood episodes, and the title described Herb as a bipolar patient.[44] Norm's coining of the name and acronym, Seasonal Affective Disorder (SAD), came later.[45] Norm made another important contribution when he wanted to contact a reporter, as he mentioned, at the *Washington Post*, but Tom and myself, being of the old fashioned school (in those days doctors didn't advertise or seek publicity), were not in favour of this. But Norm talked to Fred, Fred gave his approval, and Norm turned out to be absolutely correct in getting the story into the *Washington Post*, because I think that was a fundamentally important step in recognizing that it was not just an odd quirk in one individual but that it was a major, important disorder that affected the broad community.[46]

Follett: That deals really with the opening case. Let's think a little about the context of when all this was happening. We are talking mid-1970s, by which time we understood a lot about photoperiodism and also circadian rhythms. Might I ask the biologists present, Gerald Lincoln and Rob Lucas, to wind back to the mid-1970s when, finally, we accepted that humans were just other mammals?

Professor Gerald Lincoln: Yes, Brian and I were around in the 1970s talking about melatonin, duration of melatonin signalling and photoperiod time measurement responses in animal models. It was already evident that in photoperiodic organisms an endogenous clock-like mechanism controls seasonal biology. This was where I had a specific interest in SAD rhythmicity in man. In the animal world when you maintain organisms on constant light regimes they continue to express their seasonal rhythms due to the endogenous circannual clockwork. I remember correspondence with Anna Wirz-Justice, now working at the University of Basel, regarding a patient she had followed for 13 years with an unusual SAD syndrome.[47] The subject expressed a nice profile for a variety of different phenotypic features of SAD that were repeated each year. The intriguing feature was that this syndrome 'free ran' with a period of approximately a year and the person appeared to be in such a chronic mental state to be oblivious to

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[44] Rosenthal *et al.* (1983).

[45] Rosenthal *et al.* (1984).

[46] See page 10.

[47] See Wirz-Justice, Kräuchi and Graw (2001). Anna Wirz-Justice is Professor Emeritus at the Centre for Chronobiology, at the Psychiatric University Clinic of the University of Basel. In 1981, she and Thomas Wehr were awarded the Anna-Monika-Prize for their work in the chronobiology of depressive illness.

Figure 5: Professor Gerald Lincoln

the natural seasonal timing cues that might normally operate. We were familiar with the occurrence of free-running rhythms for the daily circadian system, so it always rang true to me to think of the SAD syndrome as a fundamental feature of seasonal biology. Man is no different from all the other animals in expressing aspects of seasonality. And when Ebo Gwinner published his book in 1986[48] we already knew that circannual rhythmicity was found in many organisms across different phyla – in plants, in insects, and even in single-celled organisms. Endogenous circannual timing is ancient and ancestral, so why not expect to find it in humans? I've listened to people talk about SAD and I always think that 'SAD' is a misnomer because it implies a negative feature of man's biology while it evolved, in my eyes, as an adaptation to cope with the winter as an anticipatory timing process. Shut down for winter and then re-activate in spring using changes in daylight as the cue.[49]

Professor Rob Lucas: I wasn't really around in the 1970s. I'm sorry if that's tactless but I guess the other sort of science that it maybe would have fitted in with was functional neuroanatomy. The appreciation that photoreception might be relevant for other things than just vision. Part of this was the discovery of projections from the retina to bits of the brain other than conventional visual

[48] Gwinner (1986).

[49] Professor Gerald Lincoln added: 'In our 24/7 world it might seem to be maladaptive.' Note on draft transcript, 4 February 2014.

Figure 6: Professor Rob Lucas

centres, in particular Bob Moore's work identifying retinal projections to the suprachiasmatic nucleus (SCN).[50] So that's a really important idea I guess that it would have fitted in with, this idea that it makes sense to have something that has a different kind of sensory capacity than what we're used to for vision, because there's more to what the retina does than just helping us to see.

Follett: Well, let me say I think this is very much at the heart of SAD. If one looks at how mammals survive winter and desperately short days then it involves very profound changes. This began with observing how the fur changed and the timing of reproduction and it is really only in the last 20 years that we have realised the degree to which there are seasonal changes in metabolism. I lecture undergraduates on this and show a group of musk ox standing in northern Norway surrounded by snow and simply not moving for weeks on end: they were not hibernating but just standing there. In today's context, what was their mind state? Perhaps to understand SAD we need to measure 'mood' in large mammals in winter because it can then be studied experimentally.

Rosenthal: If I may, sir, with respect before we move on, just comment on a few things that people have said. The first is Herb Kern. I understand he's recently deceased.[51] He was a remarkable man. Al talks about his *Science* paper

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[50] See, for example, Moore (1973).

[51] Herbert E Kern died in September 2013, aged 96.

being a paradigm shift and it certainly was. It really taught us that light can do more than just enable us to see – it was indeed a paradigm shift. But I would venture to say that there were several paradigm shifts. Before the meeting, Jo Arendt and I were talking and Jo was saying the idea had been among many people that in humans the pineal was a vestigial organ and that melatonin was not consequential, which turns out not to be true at all. So Jo's actually pursued the measurement of melatonin, to study its role in humans (and other species), even when people were saying there could be no radioimmunoassay for such small molecules, and very high level people saying that you couldn't have a radioimmunoassay. Jo just barrelled on and figured out that it could be done.[52] So there were many people who challenged conventional orthodoxies. When he wasn't depressed, Herb Kern had an irrepressible spirit and an energy. He was a short man with a crew cut and, although 63 at the time, was very energetic and very enthusiastic about our work – a total collaborator in every sense. I just wanted to pay a word of respect to a wonderful human being who also had a paradigm shift, in that he flouted convention, which was that Mother Earth was disappointing you and simply because he didn't have a psychological or psychiatric background, he saw it in physical terms as potentially driven by day length. So that's one thing. The second thing is where did basic scientists in the field fall? It's true that the emphasis had been on circannual rhythms. Like Anna Wirz-Justice's patient, Herb was one of those patients who was not typical of the usual SAD patient, but actually illustrates circannual rhythms as you can see in the diagram, the double plot in my description of his circannual cycles.[53] So some do have circannual cycles but many do not. There was, however, a lot of scepticism about whether there was any relevance in the animal world to SAD and I know that Nicholas Mrosovsky, whose book *Hibernation and the Hypothalamus* had fascinated me,[54] wrote 'Chipmunks in the Sky' in a book I edited in collaboration with Mary Blehar, and said this about SAD: Let's say you had three moles [on your body] that happened to be in a straight line, we could call that mole alignment disorder or MAD, and similarly if you get three winter depressions it could just be a coincidence.[55] However, when I spoke with

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[52] See note 17.

[53] See Rosenthal *et al.* (1983), in which Herb Kern's mood state data from his notebooks are double plotted on graphs to show the circannual rhythm of hypomania in the spring and depression in the autumn and winter.

[54] Mrosovsky (1971).

[55] Mrosovsky (1989), page 140.

Figure 7: Professor Norman Rosenthal and Professor Josephine Arendt

him off the record he said: 'You know those hibernating animals of mine, if you stress them and challenge them they look almost depressed. They do not want to be tinkered with in their hibernating state' and I think that was very apt. I feel that it's too bad that there's been a lack of cross-fertilization because there are models for depression in animals and they could be used on hibernating hamsters and have, in fact, in some cases but it hasn't really caught on. I know you said, Professor Tansey, at the beginning of this Witness Seminar, that this is not only to recapitulate history but also to stimulate future interest, and I think there is an incredible opportunity for interaction between basic and clinical scientists on this particular area.

Arendt: I'd just like to make a couple of comments, one of which is slightly off the wall because I mentioned earlier this obscure region, Antarctica, where I have done quite a lot of research.[56] People have low mood not so much in the autumn but more in the spring, and I wondered if that was evidence if you like of a retained circannual rhythm, which is appearing at the wrong time of year because they are 'out of phase' having travelled to the southern hemisphere. Secondly, I would just like to underline the contribution of Herb Kern. I was lucky enough to meet him, what a fantastic thing to do, to go and self-diagnose. Related to this field I have another example of self-diagnosis because we know that melatonin is going to come up in this SAD discussion in terms of melatonin treatment as a chronobiotic. We first described its phase-shifting effects in the

[56] See page 7.

early 1980s[57] and I was rung up by a chap called Harry Kennet in 1986: 'I'm completely blind,' he said, 'and I have non-24-hour sleep-wake disorder' – not in exactly those words as it had not been defined at that time. 'Can I have some melatonin?' he asked. And so we gave him a placebo controlled cross-over study. Melatonin stabilized his sleep-wake cycle for the rest of his long life.[58] From this and subsequent studies from our group and Al Lewy's group, we know that melatonin can synchronize circadian rhythms in humans.[59] These two self-diagnosed people have shifted the field substantially more in some respects than we scientists, it seems to me.[60]

Tansey: May I just ask a question, and that's the influence of your case study. When you wrote about Herb and you wrote your first paper actually naming SAD, what kind of influence did it have? Do you have any citation numbers? How were your professional colleagues reacting?

Rosenthal: Yes, when you look at the citations of that 1984 paper, they continue to climb, but less markedly than in the earlier years of SAD. There are about 1,200 citations of that paper more or less so far, and after 10 years the people who put out Citation Reports had me do it as a *Citation Classic*.[61] That was after ten years indicating that it was cited much more than other papers in the field. So that is some evidence. I would say that it has been much more embraced by the general public who identify with the symptoms than by the medical profession. I think that's a serious problem because Al said, and correctly so, that doctors will only recognize a disorder when they have a treatment. And I think that's partially true. I'll say it slightly differently: if they don't have a treatment they'll never recognize the disorder, or very rarely. But here's a case where they do have a treatment and they still don't recognize the disorder and I know that I'm sitting in the hallowed halls of the Wellcome Trust whose progenitor

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[57] Arendt *et al.* (1984); Arendt *et al.* (1985a); Wright *et al.* (1986).

[58] Arendt, Aldhous and Wright (1988); Arendt (1997). Professor Josephine Arendt wrote: 'He died in 2009 of prostate cancer, and he also co-authored one of our papers.' Note on draft transcript, 29 January 2014.

[59] Lockley *et al.* (2000); Sack *et al.* (2000); Lewy *et al.* (2005).

[60] Professor Josephine Arendt added: 'Incidentally I am aware that Stuart Checkley successfully treated a registered blind lady for SAD with light – but she may have had some residual light perception or indeed retained hypothalamic light perception.' Note on draft transcript, 29 January 2014.

[61] *Citation Classics,* comprising a one-page abstract and commentary, were written by authors of highly cited papers as identified by the ISI Citation Indexes. This article was cited over 380 times; see Rosenthal (1993).

was Burroughs Wellcome and whose source of revenue was the pharmaceutical industry.[62] However, the pharmaceutical industry remains a dominant force, maybe not here, but at least in the United States, in publicizing, promoting, and educating people, and insofar as light is not a drug and not patentable, there has not been this kind of flow of information by major highly funded organizations – yet fortunately I'm here in the winter with Seasonal Affective Disorder but full of good spirits and energy because I have been sitting in front of my lights every single morning. I still can't believe after decades of light therapy that medicine can come in through the eyes instead of through the mouth. It's still almost unbelievable and I know we have Jennifer Eastwood over here who is the indomitable force who initiated the SAD Association of the United Kingdom which has been the most potent self-support group for SAD and she can testify to that potency. But why isn't every person with SAD eligible for a light box by the National Health Service? It's a one-time cost and look at what it would save in terms of misery and disability and time off work and so on and so forth. I don't know how I got off onto that riff but I'll get off my soap box and pass on the microphone, I'm not at Speakers' Corner here.

Follett: If you stand off your light box [laughter] let's turn to it because I'm still back here in the early days when it was a rare disorder and it's being driven by individuals. Are they examples of a general phenomenon? One bit of evidence suggests it might be since, if you advertise, people sign up, but how did this develop here in the United Kingdom and in Northern Europe?

Ms Jennifer Eastwood: I can tell you about the development of SAD in the UK as I was one of the first patients to be tested and diagnosed here in the 1980s. Several years before we had heard of SAD in the UK, my first symptoms appeared at the age of 28 and I was diagnosed, to cut a long story short, with manic depression or Bipolar II. I wasn't convinced that I was a manic depressive because I went to some Manic Depression Fellowship meetings and knew instinctively that I was different from the rest of them.

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[62] Sir Henry Wellcome (1853–1936) created the Wellcome Trust in his will dated 29 February 1932. It endowed two research charities, one to support the history of medicine and the other to support research in medical sciences. The Trust owned the umbrella organization, the Wellcome Foundation, which had been formed in 1924 by Sir Henrry Wellcome to include his libraries, museums, research laboratories, and the pharmaceutical company of Burroughs Wellcome & Co. until it was partially floated on the stock market in 1986, eventually merging with Glaxo in 1995, and becoming part of GlaxoSmithKline in 2001. For a history of the pharmaceutical company, Burroughs Wellcome, see Church and Tansey (2007).

Figure 8: Ms Jennifer Eastwood

During the next few years, psychiatrists Dr Stuart Checkley and Dr Chris Thompson (subsequently Professors) started SAD research clinics at the Maudsley and Charing Cross Hospitals, respectively. UK medics had the same constraints as those in the USA about advertising for patients, but Dr Thompson managed to bring the attention of the media to his SAD research so his early patients, including me, were able to apply directly to him to be tested, diagnosed, and treated for SAD, probably for the first time in the UK.

Subsequently, through the SAD Association (SADA),[63] I met people older than me who had spent winters in a psychiatric institution and seem to have had a much better time than most of us who were trying to live so-called normal lives in society. SAD was certainly around but nobody in the medical profession had appeared to recognize the seasonal connection. Anyhow, I hadn't recognized my own seasonality except that, ironically, I hated the summer heat and much preferred the winter until I began to be ill.

In 1985 I went along to Charing Cross Hospital where, in order to be tested and diagnosed, I had to go off all medication. I was on eight different drugs, including lithium, and, as I gradually withdrew them, I became very ill and was admitted to hospital, whereupon a very large, cumbersome light box, made in

[63] The Seasonal Affective Disorder Association (SADA), founded in 1987 by Ms Jennifer Eastwood, is a charity run by volunteers to support and advise people with SAD: www.sada.org.uk/index.html (visited 12 March 2014).

the hospital lab, was dragged to my bedside. I started to look at it and within three to four days, felt very peculiar and didn't know what was happening. Somebody said to me: 'You're getting better', and it was quite extraordinary because I'd relied so heavily on drugs, tried psychotherapy, taken extra holidays because they always said I was overworking – I'd tried everything. But this strange box full of bright white light tubes, supposed to replicate summer daylight, was the treatment that really hit the spot.

Similar research was being undertaken at the Maudsley Hospital, where they used light rooms instead of boxes to treat patients. By the time we started the SAD Association in 1987 to raise awareness of SAD, patients were applying to be seen at either Dr Checkley's or Dr Thompson's clinic. Almost immediately, SAD and SADA attracted a great deal of media attention and we were contacted by hundreds of thousands of people, most of whom were desperate for help.[64]

I formed the somewhat cynical impression that, of those people who had been referred to a psychiatrist in the past, those that talked a lot were diagnosed as Bipolar II, and those who lay in bed and didn't talk during the winter received a diagnosis of schizophrenia. It was as if, by and large, the professionals decided that your diagnosis had to belong either with the depressive illnesses or schizophrenia-type conditions, as if there were only two areas of functional psychiatric disorders.

We at SADA soon realised that in many cases, SAD was a very serious illness and it was important that patients should be diagnosed and treated before their lives were completely destroyed and they committed suicide. Some didn't make it and we were aware of a number of suicides.[65]

It's usually seen as the winter blues that many people experience but it isn't for a number of us. I've often wondered how an animal feels with their version of SAD but one thing I know is that when an animal goes into hibernation, everything stops. They don't have to function in society during the winter and it's that that causes the problem.

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[64] Ms Jennifer Eastwood wrote: 'It was probably the first time that Seasonal Affective Disorder was described and recognized in the UK though many of our correspondents were aware of it and had self-diagnosed.' Note on draft transcript, 31 January 2014.

[65] Ms Jennifer Eastwood added: 'I remember the first time a coroner ruled that a suicide was due to SAD; it caused a stir as few professional or lay people were aware of the severity of SAD.' Note on draft transcript, 31 January 2014.

Follett: Jo, how did it strike you in the early days as it was becoming clear that SAD was more widespread here in Europe than we had thought?

Arendt: Well at that time I was collaborating with a chap called Lennart Wetterberg, I don't know if you've come across him? He's a Swedish psychiatrist; he was very, very concerned about SAD right back in the late 1970s I would say.[66] In Sweden, after the NIMH revelations, it was taken up very rapidly. I have seen that Lennart had a very interesting way of going about it. He didn't just treat people with light, he put them in an all-white room wearing all white clothes. I've no idea if there was a proper study done as to whether it was necessary to go that far but it was certainly taken very seriously in Sweden at that time. I should also say that Anna Wirz-Justice would tell you that Germany and Switzerland also took it very seriously.[67]

Rosenthal: Thanks Jo. I just want to add that it was taken very seriously. I sat in one of Lennart's wonderful bright rooms; it was a wonderful entity. I don't know if Lennart's actively working any more but in Sweden they have now declared that light therapy is not necessary or useful. There was an official document promulgated by whatever the powers that be are, because as soon as you say 'light therapy is legitimate and necessary' you are then committing yourself to a line item in the budget that's going to cost a lot of money if everybody, which is probably the entire population of Sweden, wants a light box. So they do not accept light boxes as a legitimate treatment for SAD. I looked into what it would take to try to have experts elsewhere in the world try to contest that but apparently they don't really take kindly to complete strangers giving their unsolicited opinions on matters. Jennifer, you can tell me whether the NHS will give people light boxes?

Eastwood: No.

Rosenthal: So that's a similar situation here. With that kind of situation, if you don't have the option to give people these resources, you can see why doctors would not be incentivized to diagnose the condition and recommend it as a treatment.

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[66] Lennart Wetterberg (b. 1931) is Professor Emeritus of Psychiatry at the Karolinska Institute, Stockholm and was Director and Head of the Department of Psychiatry at the Karolinska Institute, St Goran's Hospital. See the comment by Professor Alfred Lewy in note 39.

[67] Professor Josephine Arendt wrote: 'In Switzerland at least this was largely due to her efforts. She worked at NIMH with Tom Wehr, Al and Norm in the 1980s during those exciting times. Returning to Europe her enthusiasm for light treatment convinced many colleagues of its utility. In fact her advocacy continues undimmed today.' Note on draft transcript, 29 January 2014.

Figure 9: Ms Carol Barksfield

Follett: Let me go to Carol, who is from a company that manufactures light boxes.

Ms Carol Barksfield: Norm, I've been trying to get them on prescription this last year, and all I'm getting back from the NHS is that the National Institute for Health and Care Excellence (NICE) guidelines say there isn't enough research on them, and that the research is inconclusive. That's what I've had back. They want complete clinical papers, they will not take just abstracts, they want the whole thing. It's been an absolute nightmare. I've been working on it since last April.

Arendt: I think education is a problem in fact. In my various supervisory activities with regard to young doctors whom I've persuaded to do a project related to light, at least two have told me that it was not part of any medical education and if they brought it up they were told it was rubbish.

Rosenthal: If I may say, I think this really is a huge compliment to you all for having this symposium because it shows that there are people who are genuinely interested in something where there is vast scientific evidence. The number of clinical trials, controlled trials, using every manner of placebo is extensive. There was one scientist, Charmane Eastman, who was one of the last highly informed sceptics and found some – often very minor – flaw in every single study. She said every placebo was somehow defective in some way so she created her own placebo, which was a negative ion generator that had been deactivated, which was actually a brilliant placebo and she herself found the superiority of light, to

Figure 10: The Diamond Litebox and LitePod light boxes.[68]

her enormous credit because of her sceptical stance.[69] So every knowledgeable scientific sceptic has pretty much been persuaded and I think it's a sad indictment that science does not dictate policy.

Barksfield: They, NICE, just say that there isn't enough clinical expertise in the field, which I feel, when you look around here, is quite absurd, but also the light boxes are very highly regulated. They have the Medical Directive 93/42 come out of Brussels and we have to have all the light boxes tested to a very high standard.[70] The light boxes are actually tested to the same standard as heart pacemakers and those sorts of invasive devices. It's considered an invasive device because it changes the chemical balance in the brain. So we have to jump through all these hoops with the light boxes, but NICE cannot see them as a useful adjunct to treating any of these conditions.

Follett: It may all come down to politics. It's no good railing against Lady Fortune and what one often has to do is alter the political world. Maybe what we need is an MP here this afternoon who understands about legislation.

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[68] Ms Carol Barksfield wrote: 'We have three different sizes of light boxes, Diamond, which is a large box with a quick treatment time and a large spread of light; the LitePod which we believe is the most popular light box on the market; and the newest one the LitePod LED, which is very compact and as yet has not been used in any clinical studies as we have not had it long enough.' Email to Ms Caroline Overy, 7 May 2014.

[69] Eastman *et al.* (1998). Charmane Eastman is Professor of Behavioral Sciences in the Biological Rhythms Research Laboratory at Rush University Medical Center, Chicago.

[70] See Appendix 1 for the regulations with which light boxes need to comply.

Figure 11: Ms Helen Hanson

Can I go on and ask a question now? How many people are suffering from SAD? I assume that the range of suffering for many psychiatric diseases is very wide and at some point a clinician has to decide whether the person crosses a threshold or not, hence the arguments in *The Diagnostic and Statistical Manual of Mental Disorders*.[71] Is there good epidemiological evidence as to how many people are suffering from SAD; what is the gender balance; what is the relationship between the number of people who are suffering in different cultures at different latitudes? This sort of evidence would be valuable in persuading people that we are dealing with a genuinely serious problem. Is there anybody who can contribute anything on this?

Arendt: Can I just say I think it's fascinating that the Icelandic people have very few cases of SAD. And when they move to Canada likewise it's really quite rare.

Ms Helen Hanson: I think in Britain we're quite famous for having four seasons in one day and I'm sure that this lack of consistency in the weather tends to make people see-saw. Certainly that's the anecdotal evidence we're getting at SADA.

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[71] *The Diagnostic and Statistical Manual of Mental Disorders* (DSM) was first published in 1952 by the American Psychiatric Association. It is the standard classification for mental disorders. The most recent edition, *DSM-V*, was published in 2013. The third, revised third and fourth editions of the *DSM* are usually referred to as *DSM-III*; *DSM-III-R* and *DSM-IV*; the latest fifth edition is *DSM-5*. For consistency we have used Roman numerals throughout. See further discussion on the *DSM* on pages 41–2 and 49.

Rosenthal: Our group has done many, many studies on epidemiology of this condition and I think, as you so correctly pointed out, seasonality is a spectrum. The trouble is that it's not only a spectrum in the population but it's a spectrum in the individual. So you might have somebody who lives up in Canada who has got Seasonal Affective Disorder, who moves 500–600 miles down to North Carolina and has a mild case of winter blues, who then moves another several hundred miles south to Florida and then doesn't have any problem at all. There are many individual cases of that kind where the latitude influences symptoms and so, in our original study, which Siegfried Kasper, who is now Chairman of Psychiatry at the University of Vienna, and I did, we developed a questionnaire that looked at seasonality and we developed case finding criteria, and found about 4.3 per cent of people in our part of the world, which is Maryland, Washington DC.

Follett: Which is about 40 degrees north?

Rosenthal: 39 degrees. 4.3 per cent had a pure form of Seasonal Affective Disorder, as we defined it at the time, and about 13 per cent had the winter blues, which means they hadn't sought medical attention but they recognized a fall-off in function and quality of life in the winter on a regular basis. Kasper and I wrote that up and that the winter blues responded to light as well. So we had 17 or 18 per cent, or one in five that reported some problem with winter.[72]

Follett: Can I ask you whether the questionnaire placed major emphasis on the need for SAD to repeat annually, go away in the summer and reappear in the winter?

Rosenthal: It doesn't ask about seasonality in exactly that way, which would reflect the criteria for seasonal pattern, which had not yet been incorporated because it was still *DSM-III* in those days. So one in five showed some degree of problematic seasonal change at the latitude of Washington, DC. We later looked in Sarasota, Florida, New York, and up in New Hampshire, which is right at the Canadian border.[73] And in Washington DC we personally interviewed 10 per cent of the people to see to what extent our diagnoses corresponded to their questionnaire responses, and that's how we determined our case finding criteria for SAD or the winter blues. That was the Seasonal Pattern Assessment

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[72] Kasper *et al.* (1989).

[73] Rosen *et al.* (1990).

Questionnaire (SPAQ).[74] Now one of the problems in terms of determining prevalence of SAD is that depending on how strict your criteria are it's going to be less or more prevalent. If I say you've got to have depression every single winter for the past five years, for example, you're going to have virtually nobody who meets the criteria. For example, by now Jennifer has discovered that she needs to go to Malta in the winter, or wherever, to alter the course of her SAD.[75]

Eastwood: The Canary Islands.

Rosenthal: She goes to the Canary Islands in the winter, she doesn't have a seasonal depression in the winter. So these people with SAD, they're nobody's fool. They know that they've got to get out of the winter one way or another. You know they're not going to have one every winter because last winter they figured out a way to work in Miami, Florida or whatever. So the more stringent your criteria are, the more you narrow that spectrum, the less you're going to find. I think it was Dr Dixon who started off by saying this is a rather rare condition,[76] but I've spoken many times to an auditorium of say a hundred people and I'd say: 'How many of you have difficulties in the winter that are significant? Difficulties concentrating and functioning', and it's rarely less than a quarter of the room that puts their hand up. So we're not dealing with a very rare condition like Lou Gehrig's disease or maple syrup urine disease, we're dealing with something that's more like diabetes just in terms of the gut response you get.[77] I encourage people to check it out this week when you talk to others. Recently I talked in Seattle, which is very rainy, and the person who introduced me said: 'How many of you people have heard of Seasonal Affective Disorder?' The general response was 'Oh yeah'; everybody put their hand up and there was a visceral knowledge that they were signalling. So it's quite common. Now in terms of what Jo was saying about Iceland: Yes, the Icelanders seem to be protected. It may have been to their evolutionary advantage not to be too seasonal if they have to live in such a northern place. However, the Asian studies that we've done, we did them in Japan and China, also have very low rates of

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[74] See Appendices 2 and 3 for the Seasonal Pattern Assessment Questionnaire (SPAQ), and the Daily Mood Log to record mood changes over the course of a day to help interpret the SPAQ.

[75] Professor Norman Rosenthal added: 'So, by people taking remedial action, they can no longer qualify as SAD if criteria are too strict.' Note on draft transcript, 6 February 2014.

[76] See page 3.

[77] A rare disease, as defined by the European Union, is one that affects less than 5 in 10,000 of the population. For rare diseases in the UK see www.raredisease.org.uk (visited 9 April 2014).

seasonality compared with elsewhere. But there is also widespread evidence of denial of SAD in places where it's prevalent – as evidenced by the Swedes now retreating from saying that light therapy works, and the professionals here in the UK retreating as evidenced by the NICE criteria. The German-speaking world, on the other hand, has been really very supportive of seasonality and light therapy. Siegfried Kasper has led the charge there, and in Austria and Germany and Switzerland it's easy to get light boxes and people know all about it and are interested in it. So there seems to be a cultural difference in that regard.

Follett: Can somebody speak about cultures outside Northern Europe and North America? What is the situation in Japan and China? Do we also have information about Southern Europe?

Eastwood: Over the years I have been contacted by any number of people from parts of the world like Egypt and India where you wouldn't necessarily expect SAD to exist. I remember a Brazilian journalist coming to interview me so I looked at a map of the world's latitudes and saw that Brazil goes quite a long way south. There are people with winter SAD in the southern hemisphere, Australia, New Zealand, and even the Falkland Islands.[78]

I don't know about Antarctica but I know that snow makes a huge difference to the intensity of light. I'm sure that is why so many people go skiing. I think maybe the worst area for SAD is the band around northern Europe where we have short day length, poor daylight in winter, and very little, if any, snow. We also have extremely polluted skies because of the highly urbanized, industrialized society we have in Northern Europe. I've been working in air pollution science at Imperial College London for 20 years and it's taken me all that time to discover that the air pollution over London has caused there to be 12 per cent less radiant light than in the rest of the UK.

I think we would all love to have some good epidemiological studies and therefore some accurate figures for SAD prevalence, even for one country but ideally more, because nobody really knows. About 20 years ago, Professor Chris Thompson and I came independently to the conclusion that there was 1–2 per cent prevalence in the UK of people with a psychiatric disorder so severe that they couldn't function in winter. Winter blues were estimated to be about 20

[78] Ms Jennifer Eastwood added: 'People from both northern and southern hemispheres have joined SADA over the years and have tried to set up SAD support organizations in other countries but they haven't lasted.' Note on draft transcript, 31 January 2014.

per cent, and 90 per cent of the population was affected – not ill, just noticeably different in winter. I'm afraid I can't remember offhand where those figures came from.

Rosenthal: Professor Thompson has been quite critical of the Seasonal Pattern Assessment Questionnaire that has been the instrument that we've used. I think that the problem arises from the necessity for individuals to fit into the criteria created by the founders of the *DSM-IV* and *-V*; the criteria are much too rigid. I actually wrote to them but found them to be quite impervious to suggestions. I published my comments in the *American Journal of Psychiatry* and to their credit they gave me space to publish them.[79] So they're there for anybody who has any interest in the matter at all. I think often people, including scientists, respond to economic pressures primarily. So I feel that when you see the data in Sweden and the data in Britain that says people can't have their light boxes, why don't they just say: 'We haven't got enough money'? The light works and you should be entitled to it but we have a limited budget and we can't afford it. That would be honest. Nobody says you've got to pay for anything if you haven't got it in your budget to do so. But to suggest somehow that it doesn't work is fundamentally incorrect in my view.

Follett: Okay, let's think where we are. We have a disorder, which is being detected in a variable number of persons but nobody is sure about the actual incidence. If I were on NICE then I would ask questions about this lack of real numbers. Let us move to a second issue: What might be the physiological basis of SAD?

Lewy: Well, certainly with the design of the skeleton photoperiod bright light treatment of Herb Kern we were thinking of a seasonal rhythms photoperiod and possibly suppression of melatonin to shorten its night-time duration. But when I left the NIH to be where I am today in Portland, Oregon, and by the way if you want a little personal note here, I signed the contract to come to Portland, Oregon, which is a mecca of winter depression as Norm knows, two months before we treated Herb Kern with light. It's just very, very common in the Northwest, so that was a kind of lucky coincidence there. And I told the folks at Oregon: 'I want to treat this patient with light, before I actually leave the NIH. I also want to look at some blind people, because we think if light is important to suppress melatonin maybe it's a trigger for circadian rhythms.' I showed with David Newsome, eventually published in 1983, that

[79] Rosenthal (2009). See also comments on pages 41–2 and 49.

at least one blind person had a free-running circadian melatonin rhythm and at least one other blind person had an entrained melatonin that was abnormally phased (increased levels during the day).[80] And there was one other study that I won't go into now.[81] When I got to Oregon I had a conversation with Norm on the phone and he told me that he had now been talking to several of these patients and he noticed that they had trouble waking up in the winter, that they had trouble getting up in the morning and were very slow to get started. So I thought about that and I thought about all the work that Tom Wehr had done on circadian misalignment between the sleep-wake cycle, which is cued to our alarm clocks and which is dictated by our spouse, our child, our pet, our boss, our anxiety level, and is therefore loosely coupled to the body clock, and the circadian rhythms are tightly coupled to the suprachiasmatic nucleus (SCN) in the hypothalamus, and that these two sets of rhythms could become misaligned. In this case, Tom Wehr was thinking of non-seasonal bipolar depression. He published a paper in *Science* in 1979 and his theory was that the circadian rhythms were advanced, were set early, with respect to the sleep-wake cycle.[82] However, I was thinking that in SAD, circadian rhythms may be delayed, or set late, with respect to the sleep-wake cycle, and that Norm's finding of patients wanting to sleep late in the winter was an effort to try to self-treat by delaying their sleep to be in phase with their delayed circadian rhythms that were tightly coupled to the body clock that was shifting later in the winter with a short day but specifically with the later sunrise.

Follett: Can we summarize the hypothesis? There is a 24-hour clock driving the timing of sleep. As day length alters seasonally then that precise position of sleep is shifting. In most cases we don't even notice this change but it is occurring. Are you thinking that if one suffered from SAD then that positioning by the circadian system of the time of sleep was different from normal people?

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[80] Lewy and Newsome (1983). Professor Josephine Arendt wrote: 'Note that others had also reported this phenomenon (Miles, Raynal and Wilson (1977); Orth *et al.* (1979)).' Note on draft transcript, 19 June 2014. Professor Alfred Lewy commented: 'In response to Jo Arendt's reminder about the above references, which – along with related citations – were duly acknowledged in our original contributions (Lewy and Newsome (1983); Sack, Lewy and Hoban (1987)), I am also reminded that with the passage of so many years now is a good time to try to arrive at an informed and objective consensus as to which findings were key (and why).' Email to Ms Caroline Overy, 4 July 2014.

[81] Professor Alfred Lewy wrote: ' … we showed that manic-depressives were supersensitive to light and that an expanded group of normal controls suppressed their melatonin levels by 50 per cent when exposed to 500 lux light (Lewy *et al.* (1981)). Note on draft transcript, 14 February 2014.

[82] Wehr *et al.* (1979).

Lewy: Very well said. I would just like to add that there is a circadian rhythm in sleep propensity that's tightly coupled to the SCN but we don't always sleep at the time when our body clock would have us to sleep because of the other reasons I went into. So there's this mismatch between the time we're actually sleeping and are awake and when your body clock would have you be asleep and awake. And if that timing is delayed in the winter with the later sunrise, because once again it's not getting outdoor light when we wake up in the morning that is the important time cue, your circadian rhythms will drift out of phase with sleep and in some individuals this will trigger depression. So that was the theory that I called the Phase Shift Hypothesis. I wanted to include Tom's idea of a possible phase advance group, because perhaps they're cueing to the earlier sunset in the winter. However, most patients with SAD are of the phase delay type, and therefore they need light in the morning, that would be the optimal time for these patients, as soon as they awaken, if possible, to reset their circadian rhythms earlier and push them earlier back into phase with the sleep-wake cycle. That's the theory.

Follett: So you give a pulse of light, which we know will alter the phase of an organism's circadian system and you then tested in these patients whether or not a timed pulse of light could overcome SAD?

Lewy: Yes. So you mentioned earlier melatonin; is it a marker or does it do something more? And even though we give people melatonin for a number of reasons, as does Jo Arendt, we've used endogenous melatonin mainly as a marker. So we measured the melatonin rhythms in the SAD patients and specifically we measured one part of the profile, the melatonin onset. It switches on in the evening and it's a very clearly demarcated event: when the SCN signals the pineal gland to make melatonin, levels shoot up like a rocket. This was shown by basic scientists in animals. It seemed to me that would be the best thing to focus on for the whole melatonin rhythm, representing the phase of the entire set of circadian rhythms that are tightly coupled to the SCN. I got a lot of resistance on this early on. I won't mention their names but some very esteemed experts in the field said: 'Al, you've got to measure three days of data and average them to get the phase of a circadian rhythm.' Maybe they were talking about temperature or cortisol which are noisy and you need at least 24 hours of data, and you can't just use a little snippet of a window in the evening of say 6pm to bedtime, about a 5-hour window, but we did it. The other implication of the 1980 *Science* paper,[83] the light suppression finding, was that you need dim light in the experimental conditions

[83] Lewy *et al.* (1980).

when you're using endogenous melatonin as a circadian phase marker; you don't want to suppress its rise, you want to get its actual time and not a later time when you've switched the lights off. So we called this circadian phase marker the dim light melatonin onset, or DLMO,[84] and it's taken almost 30 years for it to be acknowledged as the best marker for body clock time in humans. We always thought this marker would be accepted by clinicians, especially measured in saliva, and by the way the earliest saliva work was done by Vakkuri,[85] as we were doing it mainly in plasma. It's convenient, and in saliva it's non-invasive and you can do it at home. So you have this wonderful marker that's important for a lot of reasons, such that I thought it would become a useful clinical tool. I never expected it to become the most accurate marker, and lo and behold, it is now considered to be not just the most convenient marker but as, or more, accurate than any other marker for the SCN in humans. So here in SAD we have not just a disorder but we have a marker for aspects of the disorder that we can measure in the home conveniently and hopefully this will become a standard and routine clinical test. If so, it will be perhaps the first clinical lab test in psychiatry (we can, of course, measure drug levels like lithium levels). But in psychiatry we have yet to find another biomarker that's related to a psychiatric disorder that we can measure usefully. In sleep disorders medicine it may become the first lab test, after polygraphic recordings of sleep stages, to help us objectively diagnose advanced and delayed sleep phase syndrome.[86]

Arendt: We, of course, use melatonin onset like lots of other people do. The one thing it doesn't do, though, is tell you the duration of secretion. I think that's a real pity. I've heard all sorts of people say that the reason for winter depression is long duration melatonin. And we still don't know.

Follett: The technical point here is what factors are important in the melatonin rhythm: its onset, its offset, and/or its duration. All alter seasonally. And Al is saying that it turns out that the onset in the late evening is a very good indicator and in that sense a sensible indicator to measure if you're trying to do it in populations of human beings, trying to do the duration. But I can immediately

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[84] Lewy (1983a); Lewy and Sack (1989).

[85] Vakkuri, Lappäluoto and Kauppila (1985).

[86] Professor Alfred Lewy wrote: 'Indeed, the DLMO can be used to phase type people (alone or with a sleep marker), it can be used to optimize treatment with bright light and low-dose melatonin because it marks the phase of their phase response curves (Lewy *et al.* (1992); Lewy *et al.* (1998a); Lewy (2007)), and (alone and with a sleep marker) it can monitor treatment with these phase-resetting agents.' Note on draft transcript, 14 February 2014.

see the average scientist saying: 'Well, it's not the onset, it's the duration.' Dare I ask the question: among the people who presented with SAD what was the result relative to the normal population? Were they delayed or advanced?

Lewy: I agree that most scientists would probably first target the duration of melatonin production as important in SAD, given its importance in regulating seasonal rhythms in animals. However, we published in *Science* in 1987,[87] again on a very small number of patients, eight patients that at baseline had a delayed melatonin onset compared to a group of seven normal controls and that when we gave them morning light we shifted their DLMO earlier. When we gave them evening light we shifted their DLMO later and when we gave them morning plus evening light – and now we're using evening light at 8–10pm, so it's later than with Herb Kern where I think it was falling on the dead zone of the phase response curve (PRC) – not to get into the weeds too much here, but we got an intermediate effect both in terms of the phase position of the DLMO and the antidepressant effect. The depression in seven out of the eight people in the group as a whole was significantly improved with the morning light. The mean depression rating with the evening light was no different from baseline and the combination of morning and evening light produced an antidepressant effect intermediate between that of morning light alone and evening light alone – again all very consistent supporting the idea that the mechanism is not duration of melatonin, it's the circadian phase of the body clock and its relationship to the sleep-wake cycle (we held their sleep-wake cycles constant); most of them had a phase delay in their circadian misalignment and morning light is the best time to correct that phase delay by providing a corrective therapeutic phase advance.[88] Then just to skip ahead here, but others may want to intervene a little bit, to 1998, Norm mentioned the work of Charmane Eastman, as well as Michael Terman, and our group published three papers back to back in the *Archives of General Psychiatry* where the shared conclusion was that morning was the best time to treat most patients with SAD.[89] Since then I believe, others may differ here, that is the consensus.

Rosenthal: Yes, two points that Al raises that I really want to support and endorse. That is that the morning light has proven to be the most effective time aside from whatever mechanism might be involved. There's consensus in the field and Al absolutely was the first to say so, and I want that to be on the record. I also want to

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[87] Lewy *et al.* (1987a).

[88] Professor Alfred Lewy added: 'This study also identified one individual who preferentially responded to evening light (Lewy *et al.* (1987a)).' Note on draft transcript, 14 February 2014.

[89] Eastman *et al.* (1998); Terman, Terman and Ross (1998); Lewy *et al.* (1998b).

address the segue by which the question of mechanisms was introduced: that is, how can we establish the prevalence of this condition if we don't know the mechanism, as we do with HIV, for example? But in that case we would never be able to have the prevalence of any psychiatric disorder because there is no psychiatric disorder where there is a blood test or some other definitive acid test. Researchers thought, once upon a time, that the so-called dexamethasone suppression test was the litmus test for depression, but it turned out to be non-specific. The entire psychiatric canon hangs upon conditions that exist only in syndromal form, absent of any biological marker, so it doesn't really seem fair to hold SAD to a higher standard. Another point, which has been introduced by Jo Arendt, relates to what we've heard throughout the day: that anything that happens in animals also happens in humans; that this notion that somehow, because we're so smart, we've escaped our biological heritage, is not established and doesn't hold up. In the animal kingdom there are essentially two oscillators, one that tracks dawn and one that tracks dusk, and depending on the duration of the day length these oscillators move apart in the summer and together in the winter. In fact, Tom Wehr in our group used methodology whereby he put people who had been sleeping or in the dark on a certain regimen, 14 hours in the dark, 10 hours in the light versus 8 hours in the dark and 16 hours in the light – a winter versus a summer photoperiod. They slept that way for weeks. Then he brought them in for a 24-hour period during which they were in very dim lighting conditions in which case the thumb print of the photoperiod of the previous couple of months would manifest itself in the melatonin duration. These were normal controls by the way. And what he found was that, as predicted, in the winter time the melatonin duration increased and in the summer time it decreased. In other words, melatonin profiles changed with photoperiod exactly as they do in sheep.[90] However, what happened when he took these same individuals in winter and in summer when there was a natural photoperiod and scotoperiod corresponding to his experimental conditions, there was no difference between summer and winter melatonin profiles. So, what was essentially happening was that their ordinary daily use of artificial light, which was not regulated but was just as normal, was actually being perceived by these people – not visually but at some central location, be it the SCN, be it the pineal, whichever circuitry was involved – as though it was real summer time. They showed no difference in melatonin profiles between summer and winter under naturalistic conditions, but they did show a difference when they had to spend 16 hours in the dark. What that suggested was that the natural capacity of the human circadian

[90] For melatonin profiles in sheep, see, for example, Lincoln (2006); Lincoln and Hazlerigg (2010). See also note 97.

system to express photoperiod is preserved and intact, but normally overwritten by exposure to artificial light. Then he took patients with SAD, summer and winter in naturalistic lighting conditions, and what he found was that in the winter compared to the summer the duration of melatonin actually expanded under the 24-hour constant conditions, without their having undergone any experimental manipulation ahead of time.[91] So, in other words, the way we interpret those data is that somehow people with SAD have a higher threshold for perceiving light in whatever circuits and portions of the brain are relevant. They do not perceive the light as sharply, which would explain why they need extra bright light. The ordinary artificial light does not influence their duration of melatonin secretion and thereby influence their oscillators in a way that it does with healthy individuals. So Wehr and I have a somewhat different explanation from Al's for the mechanism of what's happening to the circadian system and how that's causing the symptoms of SAD.

Follett: Not so much the duration of photoperiod but the intensity, the responsiveness to the intensity of light. We know that in circadian theory.

Lucas: I'm not sure if I'm allowed to ask a question but it interests me, the possibility that the idea of mechanisms here might reflect the time in history when SAD was described. That was a time when circadian and seasonal rhythms were of great biological interest and those concepts were starting to be more widely accepted. Where actually what we have is the correlation of light and the effect, and perhaps light might have influences other than on the circadian clock or melatonin rhythms that could explain this. Maybe that's something that we understand more recently because of the appreciation that there are visual pathways influencing, quite fundamentally, aspects of physiology and behaviour that may not necessarily be by the clock.

Lewy: Tom Wehr made a very important discovery in the sleep cycles of individuals under artificial very long nights and it should also be noted that they were in absolute darkness: no reading lamps, not a flicker of light.[92] He made a brilliant discovery that the sleep bout changed into two bouts: an early bout and a late bout separated by a few hours of what he called quiet wakefulness. A lot has been written about this over the years as perhaps something that was biologically programmed when we evolved as a species, that this was a time that we needed for certain thinking or activities or something where we certainly didn't get up, as there were a lot of predators out there at night that we didn't want to encounter. So

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[91] Wehr (1991, 1992).

[92] Wehr *et al.* (1993).

it stimulated a lot of very interesting anthropological and philosophical thinking along those lines. But I do not agree that there are two loosely coupled oscillators that control the melatonin production. Helena Illnerová from Prague has done a lot of brilliant work on this, but she's been studying rats.[93] It's very interesting what we can and cannot translate from animals to humans, and what we can reverse translate from humans to animals. I'll give you an example of the latter as a little bit of an aside here. After we showed that bright light could suppress melatonin in humans, Russel Reiter took some squirrels out of the wild and showed that they were insensitive to ordinary room light just like humans,[94] as we had speculated in the last line of that *Science* 1980 paper.[95] We're adapting to bright light exposure all day long. We come indoors and are tested with laboratory light that is nothing in intensity compared to what we've been experiencing outside. It's sort of a short-term adaptation. There are several papers out on this topic now, a variety of investigators looking at adaptation and short-term history of light exposure in humans. I'm sure Rob can comment on that as well. When Helena tried to test this amazing, clear-cut demonstration of two oscillators in rat – an evening oscillator regulating the rise of melatonin and a dawn oscillator regulating the fall of melatonin – it hasn't been nearly as demonstrable in humans as it has been in rats.[96] I would say that if there are two oscillators controlling the melatonin rhythm in humans then they are tightly coupled and do not change their phase relationship to each other very much during the usual experience of the natural and artificial light exposures across the year. In fact, in Tom's paper I think they changed only by less than an hour in the natural photoperiod, which is much less than we see in sheep.[97] And it was more in the males than in the females.[98] And one of the things we skipped over earlier is that most patients with SAD are female.

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[93] See, for example, Illnerová and Vaněcek (1982).

[94] Reiter *et al.* (1982).

[95] The last line of the paper reads: 'Perhaps, by distinguishing among different light intensities, humans have adapted to artificial lighting while remaining sensitive to the natural light-dark cycle.' (Lewy *et al.* (1980), page 69).

[96] Jelinkova-Vondrasova, Hajek and Illnerová (1999).

[97] Professor Josephine Arendt wrote: 'In 1979 and 1981 we reported extended duration of secretion in Suffolk Cross sheep living outside in winter with two peaks in some individual animals approximately nine hours apart and only one peak in summer. We have also observed two peaks in some human subjects without reference to season (Arendt (1979); Arendt, Symons and Laud (1981)).' Note on draft transcript, 29 January 2014.

[98] Wehr *et al.* (2001).

Eastwood: May I just reply to Al's last comment? The female/male ratio published in research studies was usually 4:1.[99] SADA used to do an annual questionnaire, which usually attracted 500+ responses, and the results were professionally analysed and sometimes published or presented at conferences. SADA's female/male ratio was invariably 3:1, occasionally 2:1, simply because men in general do not like admitting to mental illness even if it's from an external or environmental cue like SAD, and they are more reluctant to seek treatment or enlist in research studies. We used to find that, winter after winter, men would write to SADA, saying: 'Help! Our wives are going to leave us/our secretaries have left us/I'm getting the sack', and it was only because they were absolutely desperate that they were pushed into coming forward and saying that that they had something wrong with them.

There are many conditions where women are seen to be predominant but it is partly because women admit to symptoms and seek treatment. There are obviously more females with SAD because there's a strong link with gynaecological/endocrinological disorders, e.g. postnatal depression is often a starter for SAD. It doesn't matter how weird our circadian rhythms are, this illness is somehow triggered at a particular age in particular people, and its onset is at different times of life. For example, men sometimes become depressed when they give up work. They don't realize that they've probably been depressed for years but they've taken it out on their families and colleagues.

Follett: We must move off what you might call the circadian basis of some of SAD and move to diagnosis and therapy. SAD is starting to get traction as a genuine syndrome. There may be disagreements, or not, and these are reflected in the *DSM-V* manual. But in the most recent edition there is a clear set of statements about SAD. It is a recurrent major depressive disorder with a regular temporal relationship between the onset of major depressive episodes at a particular time of year. They do not lock it to winter but we're focusing particularly this afternoon on winter 'e.g. in the fall or winter'. And they want to exclude from this cases where there's an obvious effect of seasonally related psychosocial stress, people who cannot gain employment in winter because their job is summer-related. And also they use the term 'full remission' or at least a change from major depression to mania or hypomania.[100] Presumably these diagnostics arose obviously after the phenomenon had been discovered.

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[99] See, for example, Leibenluft, Hardin and Rosenthal (1995); Lucht and Kasper (1999).

[100] See American Psychiatric Association (2013), pages 153–4.

Rosenthal: I should start by saying that this is an unhelpful list of criteria and let us say that in the last two years my friend Jennifer – who has got one of the most classic documented cases of SAD on the records happened to go to the Canary Islands last winter and thereby escaped depression entirely but had had a depression every winter before that for the previous 19 years – would not meet the new criteria for SAD, because in the last two winters she would not have had two depressions. So that fact of needing it to have happened in the last two winters is entirely arbitrary without any basis in science and I could go on and on about problems with the *DSM* criteria. This issue of the seasonally variable occupational thing or seasonally variable precipitate has been in the canon of the *DSM* since *DSM-III-R*, the revised version of *DSM-III*. And that goes back probably to the late 1980s.[101] I don't know of anybody, myself included, who has ever seen a case where there is a reliable psychosocial variable that has explained the phenomena of SAD, so here's a criterion that nobody's ever seen but it's stayed in the documentation. In any event this is not much different from what was initially entered in *DSM-III-R*. There was a twist, which was worse, when my colleague Bob Spitzer, who was a major nosologist,[102] tried to quantify the necessary number of depressive episodes by saying there could be other depressions but there had to be at least a 3:1 ratio of seasonal to non-seasonal, that turned out to be almost impossible to implement. So the current definition has been how it has stayed. Incidentally, sometimes SAD patients take antidepressants before winter, which prevents the expected depression. My colleagues and I have actually done a study with Wellbutrin (bupropion) where we found that it prevented winter depression in a significant number of cases without any light therapy in a double-blind controlled study of a thousand subjects.[103] We showed that it pre-empted the depression. Would that mean that that person in the study no longer suffered from SAD? According to these criteria, it would.

Follett: Thank you. You have advanced us onto the specific therapies and also introduced some pharmacology as distinct from light therapy, but how do the rest of you view these various therapies? We can now move the discussion, as Norman has done, onto what can we do for people who suffer from this?

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[101] *DSM-III* was published in 1980 and the revised edition, *DSM-III-R*, in 1987.

[102] Robert Spitzer was Professor of Psychiatry at Columbia University, New York and was chair of the committee for developing *DSM-III*.

[103] Modell *et al.* (2005). Three randomized placebo-controlled prevention trials were carried out which resulted in a risk reduction of 44 per cent for patients taking Bupropion XL. For further comments on Wellbutrin see pages 44 and 48.

Lewy: You can use melatonin as a therapy, and that's a little counter-intuitive if you're a believer in the photoperiodic hypothesis. We showed in the *Proceedings of the National Academy of Sciences* in 2006 that asymmetric lengthening of the melatonin duration in SAD patients improved their depression, because when we gave it in the afternoon they phase advanced.[104] So low-dose melatonin (0.3mg was the maximum daily amount we used in that study) was given in the afternoon to extend the duration of the melatonin profile in order to produce a chemical dark signal to the body clock before signalling an earlier sunset. So we 'advanced sunset' with low-dose melatonin rather than advancing sunrise with bright light, and thereby caused a phase advance in the body clock relative to the sleep-wake cycle.[105] So low-dose melatonin in the afternoon is an effective treatment for most patients (who are phase delayed). There is a smaller subgroup that positively responds to the melatonin administered in the morning.[106] In either case, we're lengthening the duration of melatonin, and this study convinced me that an increase in the duration of melatonin production is not causing people to get depressed in the winter and shortening it is not related to treatment with bright light. So, in fact, low-dose melatonin treatment can be used instead of light treatment. They're both shifting the circadian clock, but you have to give them at opposite times of the day.

Follett: So the key thing is either light or melatonin as a means of shifting.

Eastwood: Over 25 years SADA has studied and advised on the treatment of tens of thousands of people. Although we don't have many scientific publications, we have had huge numbers of people, probably well over a million. I started SADA in 1987. After the first radio programme, which took place with Professor Thompson, we began to get thousands of enquiries from the public. There was a period of several years when, between November and February, I sometimes received a thousand or more letters a day, delivered in sacks from the post office. Nobody really believed me but I took a sack of letters to a meeting, emptied

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[104] Lewy *et al.* (2006).

[105] Professor Alfred Lewy added: 'In order to achieve overlap between the exogenous melatonin and the endogenous melatonin profile so as to optimize its phase-shifting effect (Lewy and Sack (1997)) the low dose was divided into even smaller equal parts, two hours apart, so that the first of these could be administered in the early afternoon and the last of these less than two hours before the endogenous melatonin onset.' Note on draft transcript, 14 February 2014.

[106] Professor Alfred Lewy wrote: 'as large as one-third of SAD patients, larger than the 1/8th proportion who preferentially responded to evening light in the 1987 study (Lewy *et al.* (1987a)). Note on draft transcript, 14 February 2014.

them onto the floor, and showed my colleagues what was going on. Most of the writers claimed to have some degree of SAD and I know you can discount a large number of those as manageable, but nonetheless distressing, winter blues but some of the things I read were horrendous. When I see that there's not a single UK psychiatrist in this room, it makes me wonder what I've been doing for the last 25 years because it's really tragic. There's a hell of a lot of misery out there.

Tansey: Can I just say it's not for want of trying to find them, nor for inviting them.

Eastwood: Oh I know.

Tansey: I just want to put that on the record.

Eastwood: Yes, sorry, anyway I'm digressing slightly.

Follett: Back to the treatment.

Eastwood: Bright white light via the eyes is the most effective treatment for the majority of people with SAD, certainly in the UK. The problem with it is compliance, using it enough throughout the winter. Medics will tell you that with any treatment, the biggest problem is compliance. However, it is often difficult to use enough light treatment to stay well throughout the winter. We all say how wonderful it is and that it's only 30 minutes at the beginning of the day but I'm afraid that's not the reality for most of us. People with full-blown SAD need at least two hours' treatment every day with 10,000–20,000 lux and even that may not be enough.[107]

Those people who find that light is not enough or want a back-up, supplement it with whatever drugs are recommended or available. Bupropion (Wellbutrin), which is the main drug of choice for SAD in the USA, is also prescribed in most north European countries.[108] However, in the UK, bupropion is only licensed as Zyban to help people give up smoking! My GP has to go along to the local primary care trust (PCT) every few months and make a case as to

[107] Ms Jennifer Eastwood wrote: 'We need to use it every day (the occasional day off is usually okay) from, in some cases, September to April.' Note on draft transcript, 31 January 2014.

[108] Bupropion was patented in 1969 by Burroughs Wellcome (Wellcome Foundation – which became part of what is now GlaxoSmithKline). It was approved by the FDA in the USA as a treatment for the prevention of SAD in 2006. For a review of the treatment see, for example, Niemegeers *et al.* (2013). See further comments on Wellbutrin by Professor Norman Rosenthal on pages 42 and 48.

why I have to have bupropion when there are so many lovely antidepressants around. As you can see, I'm someone who has learned the system and jumps up and down till she gets what she wants, but the majority of Brits don't and they put up with what they are told. However, there are a number of other drugs, in particular selective serotonin reuptake inhibitors (SSRIs), many of which are very effective.[109] They came on the market about the same time as light therapy so the combination of them was pretty fantastic, certainly for the psychiatric element of SAD. Personally, I don't think drugs deal with the real biological depth of SAD, the cognitive and vegetative symptoms that make you only a fraction of yourself during the winter. I've studied this for many years in myself and a selected group of people that I've kept an eye on over the years and there's something about light that, if you use enough of it, it does the trick.

The only thing that *really* gets there, as Norman says, is going to the Canaries or somewhere much nearer the Equator. If I'd known about SAD earlier, I would have left the UK and never come back in the winter. The trouble is that by the time you find you have SAD, you've made a life here. It is purely and simply about moving nearer to bright daylight and long daylight hours.[110] I don't know anybody who has been diagnosed with SAD that is any different.

Those are basically the treatments. We've tried pretty well everything, including complementary treatments, though few of the therapists will ever engage in any research, they all just come along and think they can cure you. Psychotherapists are the worst; the ones I've met have almost all said: 'Oh I'm sure we can cure you of this', and I've never known anyone to be able to do it. I've had about 20 years' psychotherapy and it was a great help but it doesn't treat SAD. So that's it.

Follett: Well, we've got other people here in the room who undertake SAD research: Ilana and Peter Crome, for example, who are researchers.

Professor Ilana Crome: We are here as very long-standing friends of Norman. I am a psychiatrist and I did work with Stuart Checkley at one time but I moved on into addiction psychiatry in the mid-1980s. But I will say a few

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[109] For the drug treatment of SAD, see, for example, Winkler *et al.* (2010). For a discussion of SSRIs and depression, see comments by Professor Philip Cowen and others at the Witness Seminar on drugs affecting 5-HT systems (Overy and Tansey (eds) (2013), pages 115–22 *passim*).

[110] Ms Jennifer Eastwood wrote: 'Many of us manage a few weeks' holiday in the sun but the problem is that when you return to the UK, the symptoms come back after 3–4 days so, in theory, you need to move south by the end of October and stay till March at earliest, as the nineteenth-century psychiatrist Esquirol advised. This is not conducive to family life, work etc.' Note on draft transcript, 31 January 2014.

Figure12: Professor Ilana Crome

things. Education is a big issue that has come up, I think that Jennifer and Norman have alluded to that, but medical students get very little education in psychiatry generally throughout their training and I don't think SAD would be high on the agenda of any training scheme because there are many people who say there are a lot more disorders that a medical student needs to be taught. So I think that is one reason why you would be confronted by psychiatrists and other medical practitioners and their teams who know very little about it and lack the confidence to undertake or suggest any treatment. Doctors are driven by NICE and if NICE is not going to recommend it, it's a real issue. So there are a lot of aspects that can lead to the fact that patients seeking help won't get the right kind of help. My own interest is psychiatric co-morbidity so what I haven't heard from anybody is what the other psychiatric disorders that may be associated with SAD could possibly be because there is a great deal of physical and psychiatric co-morbidity in individuals who have psychiatric disorders. That's something of interest to me. Finally, I'd just like to say, I don't know what the relevance in terms of aetiology of SAD may be for affective disorder generally or other co-existing disorders. So maybe somebody can answer that.

Follett: Let's first go to Jo before we come to answer your question.

Arendt: I was just going back very briefly to treatment, and to ask Al in particular: you know that the melatonin agonist agomelatine is actually registered for

depression.[111] Do you think there is an element of that in the effects of your treatment with melatonin via 5-HT_{2C} receptors?[112]

Follett: And what's the history of this?

Lewy: Servier (by the way full disclosure, I consult for Servier) has a melatonin agonist that they've patented (agomelatine) that shifts circadian rhythms just like melatonin, but also affects some serotonin receptors. The thinking of the Servier people is that agomelatine has a dual mechanism for its antidepressant effects, that both its circadian phase-shifting effect is important, but also its serotonergic effects.[113] Now Servier is using their drug, as Jo mentioned, for non-seasonal major depressive disorder, and I think it's sold in 75 countries around the world. Is it in the UK?

Arendt: I believe so.[114]

Lewy: It is not sold in the USA or Canada. In 2009 we published a paper – Jon Emens is the first author – showing that 17 non-seasonal major depressives had a correlation between the amount of phase delay in the melatonin onset relative to the sleep-wake cycle and the increase in their depression ratings.[115] Then in 2010, three groups published further findings, including successfully treating non-seasonal depressives with melatonin to advance their body clock.[116] Nothing more has appeared since 2010, and I'm not sure what the reason is. In any event there may be a component of circadian misalignment in other disorders besides SAD, such as non-seasonal major depressive disorder. Our latest finding, which is due to appear in early 2014, is that anxiety symptoms in SAD seem to be related to circadian misalignment.[117] And the Servier folks

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[111] de Bodinat *et al.* (2010).

[112] The British usage of the term 5-HT and the American usage of the term serotonin for the same compound has been maintained throughout the transcript.

[113] Professor Alfred Lewy added: 'To the best of my knowledge, melatonin only has the phase-shifting effect and not the effect on serotonin receptors.' Note on draft transcript, 24 February 2014. For additional discussion of agomelatine, see the comments by Professor Daniel Hoyer at the Witness Seminar on drugs affecting 5-HT systems (Overy and Tansey (eds) (2013), page 114).

[114] Agomelatine, marketed as Valdoxan, was approved for use in the European Union in 2009. For a review of its antidepressant efficacy, see Taylor *et al.* (2014).

[115] Emens *et al.* (2009).

[116] Buckley and Schatzberg (2010); Rahman, Kayumov and Shapiro (2010); Hasler *et al.* (2010).

[117] Lewy *et al.* (2014).

also find that agomelatine is effective in anxiety. So there's a lot more research that needs to be done on the circadian misalignment component in various psychiatric disorders and on what sort of specific features it is closely related to. Is it depression? Is it anxiety? Both? There are some other features of psychiatric disorders that may have a circadian misalignment component as well.

Lucas: Sticking on the therapy question. The defining feature of SAD is that light is the most effective therapy, but I wonder how well defined the light that you need is? To be fair to NICE, I'm not sure that I could tell for sure what the efficacy of any given light would be. We talked about 2,500 lux. I'm sure I could give you a 2,500 lux light that wouldn't be very effective if it did not contain the right wavelengths.

Follett: Do we know about whether there are particular aspects of the spectrum that are more effective or less effective? In developing light therapy, you must have tried a number of different lights?

Rosenthal: If I can just follow up on a couple of threads here. The first is treatments of SAD other than light therapy and, in fact, clinically speaking, many antidepressants are very effective, including the serotonergic antidepressants, the selective serotonergic reuptake inhibitors, and the serotonergic and norepinephrine reuptake inhibitors. Wellbutrin, which you've heard about, is a norepinephrine and dopamine reuptake inhibitor, so all of these three major neurotransmitters that have been implicated in depression are helpful when they're tinkered with by the various antidepressants in people with SAD. However, this has not been done in large-scale studies. When we came to look at Wellbutrin as a prophylaxis for SAD, I was a consultant to GlaxoSmithKline, which was the distributor of Wellbutrin (which has subsequently gone off patent in the United States). We had to go before the FDA and get authorization to regard SAD as a distinct treatment entity that was eligible for being studied in its own right, so that if researchers were to show an effect of a drug, they would then be able to advertise it specifically for SAD.[118] Up until that time SAD had been lumped together with the rest of depression and therefore there was nothing in it for any of the pharmaceutical companies to study it selectively and specifically. So that's why these other companies never had done that. But the FDA said: 'Yes, SAD is a specific distinct entity. You can study it and you can advertise specifically for SAD and you can do it prophylactically',

[118] Wellbutrin was approved by the FDA for patients with SAD in June 2006. See also comments on pages 42 and 44.

which was a big step. But the serotonergic drugs do work practically speaking. Now to get back to Rob's excellent point earlier: light is working on a lot of things other than the circadian system and that's really important to note. For example, the retinohypothalamic tract that goes to the pacemaker (SCN) works via glutamate, and one of the big stories in modern antidepressant treatment is the use of ketamine for highly refractory depressions.[119] And ketamine is known to work on glutamate receptors. In addition, the pacemaker is gated by serotonergic inputs so when you've got something that's as important as light and dark that we've evolved with over all these millennia, you can imagine that light is having many, many effects. As Jo Arendt and I were talking about in the break, people placed in light are immediately activated. You know if you keep bright light on it will be hard to go to sleep at night. Now that's too quick to have a pacemaker effect, presumably it's just an activating principle. That's why they have bright lights in supermarkets because you'll buy more stuff because you get activated. So what I'm really saying is light is doing a lot of things. Now clinically this has been exploited in terms of premenstrual syndrome. My colleague, Dr Barbara Parry, who worked at the NIMH, has shown that premenstrual syndrome can be prevented and treated by the use of light, including evening light.[120] Likewise, Dr Raymond Lam up in Vancouver has shown that bulimia can be strongly influenced by the use of light.[121] Now both of these may be being helped through serotonergic influences of light. For example, there's a *Lancet* paper where they cannulated the jugular vein of normal volunteers and measured serotonin output coming from the brain and showed that, in normal volunteers, serotonin concentrations in blood were highest on the brightest days.[122] But there are so many neurotransmitters that I'm sure we have hardly even touched on the full spectrum. I think we probably just have seen the tip of the iceberg because it's what we studied, but there are probably a lot of other things that are influenced by light. The other thing I want to mention just getting back to the *DSM-V* criteria is that they require you to have SAD only if there's complete remission or hypomania in the summer whereas many, many people with SAD do not completely return to a normal mood in the summer time. You can comment on this maybe, Jennifer, but a lot of people

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[119] See, for example, Salvadore and Singh (2013); Browne and Lucki (2013).

[120] See, for example, Parry *et al.* (1987).

[121] See, for example, Lam (1989); Lam *et al.* (2001).

[122] Lambert *et al.* (2002).

have got a sort of chronic low-grade depression that gets much worse in the winter time and clearly all of the work that's been done in SAD is applicable to that group of people as well. They should not be excluded.

Hanson: I would like to add that the awful summer of 2012 was a very good example of what you've just been speaking about. We had continuing press interest, rare in summer, and also a lot of reports from sufferers that their symptoms had either not gone away that summer or that they'd had serious lapses.[123] We're starting to feel in SADA that the division into seasons is a bit arbitrary and doesn't fully explain the nature of the condition.

Rosenthal: This is a very, very important point because the syndrome is not just a seasonal syndrome, it's a light deficiency syndrome, and what we have seen with global warming and summers being intensely hot in the United States is that a lot of people with SAD are staying indoors in the air conditioning and putting their blinds and their shades down so that the sun doesn't overheat the interiors. And in doing so are getting light deprived and paradoxically are having winter type depressions in the summer because of global warming.

Barksfield: Yes, Norman, we've seen the same thing and what we've found as well is that a lot more office buildings are being built with tinted glass so a lot of people, even though they're sitting next to a window working, even if it's summer, they're still finding the symptoms or still experiencing the symptoms of SAD because they're still not getting any light during the summer either. So we have found as a company it's much less seasonal and more of a year-round thing.

Hanson: I'd like to add that we're particularly concerned about children and young people. We've had quite a few people writing into us about the fact that they notice when they go into their children's schools that these days they're working at screens in darkened rooms with the curtains drawn, blinds down, and so on. The whole question of environmental light and its relationship to health is something that we just don't seem to take on board in the UK. We may be laying trouble for ourselves. I think they are much more aware of environmental light in the workplace in Germany, for example, and in the Scandinavian countries. We're behind the times in this respect and should be addressing the issue.

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[123] In the UK, the summer of 2012 had below average temperatures for June, July, and August, was the wettest since 1912, and had 82 per cent of the normal sunshine; see the statistics at the Met Office website at www.metoffice.gov.uk/climate/uk/2012/summer.html (visited 17 March 2014).

Lewy: I agree with what's being said about light in the workplace and in the home, but generally outdoor light has to be experienced outdoors to be chronobiologically influential. The window acts like a point source for sunlight, and given the inverse square law between experienced light intensity and the distance your eyes are from the light source, unless your nose is almost pressed up against the window pane and sunlight is directly streaming in, you're probably not going to get bright enough light indoors to do much to your body clock. But getting back to a couple of other points here: I agree with Norm that there is an energizing effect of sitting in front of a light box.[124] I think we all agree there. But until a specific mechanism is identified, I have to put that effect in a slightly different category than the phase-shifting effects of light. And so I tell my patients: 'You need the light in the morning or a few of you need it in the evening but don't do it at both times. More light does not necessarily mean a better effect. If you like the immediate effect of the light and you really want more light, add it in the middle of the day, in the dead zone of the light phase response curve where it won't counteract the phase-shifting effect of light that is important for its antidepressant mechanism.' But getting back to Rob's point about what kind of light: the light intensity should ideally be between 2,000 and 10,000 lux. I think we've pretty much capped it at 10,000 lux, because we're still a little concerned about doing damage to the eyes at higher intensities. Some people need to sit in front of it, at least to start out with, for 2 hours a day, ideally shortly after awakening, and then they can cut down the duration to 20–30 minutes once they respond. The eyes have to be open, of course. We don't have them stare at the light; we have the light coming in from an angle, from the side or, if you're reading and your head is tilted down, from above. So that's been the standard for a couple of decades now. With regard to the light wavelengths, which you are, of course, an expert on, Rob, George Brainard and I published the first study of different wavelengths suppressing melatonin in humans in 1985 and we found, in this early study, that the greatest suppression of melatonin production was at 509 nanometers, which is blue-green light.[125] And, of course, the melatonin suppression test tells us how the light's going to be effective in causing phase shifts. We're not saying the suppression of melatonin is necessarily involved in anything, except telling us that this intensity and wavelength composition will be effective when used in the morning to phase advance the clock, or in the evening to phase delay

[124] Lewy and Sack (1986).

[125] Brainard *et al.* (1985).

the clock. Now perhaps, Rob, you could explain to us what's been happening with the excellent work of you and your colleagues on melanopsin and which wavelengths are most effective in stimulating melanopsin, which is the most important photoreceptor for these effects.[126] But before getting into that I think there are studies with green light, which is close to 509 nanometers, and there's a controversy over pure blue light being bad for the eyes, that you might want to comment on.

Lucas: Yes, I'm happy to comment. Jo should also speak about her action spectrum for melatonin suppression, which was published in 2001, is that right?

Arendt: Exactly the same day as …

Lucas: As Brainard's, exactly yes.[127] [Laughs]

Arendt: I think there was some collusion of journal editors there.

Lucas: Okay, at one level this comes to very fundamental questions of mechanisms and how light is detected because, of course, the spectral sensitivity of rod and cone photoreceptors is very well established and known for a long time, and if they were the only players in the system you could make some pretty reasonable assessments of what wavelengths of light would be important. So the discovery that there's an additional photoreceptor system involving melanopsin and these intrinsically photosensitive retinal ganglion cells (ipRGCs) is an important underpinning science for this field. In terms of spectral sensitivity of that photoreceptor, some of the earliest evidence that this was a sort of a blue light photoreceptor came from work in retinally degenerate (RD) mice in the late 1990s. Ebihara's lab published some work in RD mice, which have almost no rod and cone photoreceptors left and looked at circadian phase shifting and reported a maximal spectral sensitivity at 480 nanometers.[128] That's important because none of the mouse photoreceptors had a peak around then. But that work was not as influential with hindsight as maybe it should have been because there was other work on RD mice reporting a different spectral sensitivity, leaving the literature a bit confusing. In 2001, we published a paper showing that the pupil light reflex in mice lacking rods and cones had peak sensitivity around 480 nanometers.[129] And since then that figure

[126] See Lucas *et al.* (2014).

[127] Brainard *et al.* (2001); Thapan, Arendt and Skene (2001).

[128] See, for example, Yoshimura and Ebihara (1996).

[129] Lucas, Douglas and Foster (2001).

has proved to be retained for melanopsin in all species looked at so far. So in 2002, David Berson reported the first description of these ipRGCs in *Science* and he showed in rats that they had a peak sensitivity around 480 nanometers[130] and subsequently Dennis Dacey and Paul Gamlin showed in primates that they were 480 nanometers[131] and Paul Gamlin showed for pupil light reflex for humans that there was a 480 nanometer component.[132] Then just last year we showed for human melanopsin protein expression *in vitro* that it had peak sensitivity at 480.[133] So I think most people now would say that this melanopsin photoreceptor peaks in the blue part of the spectrum but because of the way the opsin works it does, of course, absorb over quite a wide wavelength range so there's nothing magic necessarily about blue, it's just the blue is slightly more effective than green, or violet for the melanopsin system. Now, relating that to Seasonal Affective Disorder, or indeed to phase shift in the clock, or to melatonin suppression, we have to consider the possibility that it's not just melanopsin that contributes to these responses but also potentially other photoreceptors. We know that this is true from animal experiments, from lots of people's work that the ipRGCs respond to light both because they have melanopsin and because they receive input from rod and cone photoreceptors. I think it's fair to say that at present we aren't sure as a field exactly what determines the relative reliance of downstream responses on those spectrally distinct inputs. Therefore it's hard to be sure *a priori* what wavelengths your biological system would be responsive to under a particular set of circumstances. So as part of that, of course, one would really like to know what's the spectral sensitivity of biologically relevant events in humans, and it would be great to know what that was, for example, for treatment of SAD. Jo's lab and Brainard looked at this for melatonin suppression and perhaps I should pass the microphone onto you, Jo, for that.

Arendt: We played around with different intensity and spectral characteristics of light in the 1980s and 1990s. The lead person on the action spectrum project was my colleague Debra Skene with our PhD student Kavitha Thapan, and I was just the Principal Investigator. We found a peak of melatonin suppression at 465 nanometers in our first shot at this, but that was then adjusted by further

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[130] Berson, Dunn and Takao (2002).

[131] Dacey *et al.* (2005).

[132] Gamlin *et al.* (2007); McDougal and Gamlin (2010).

[133] Bailes and Lucas (2013).

points on the curve to very close to 480.[134] This also appeared to be the peak for phase shifting and alertness in our work and that of others.[135] My interest in this is, of course, how can you make use of it in real life and I am much too old to wait for all these mechanisms to be sorted out. In our group Philips Lighting have worked very hard with Debra and Benita Middleton and colleagues to look at 'blue enriched' light compared to standard white in a variety of circumstances in old people's homes, for example.[136] But we have not studied SAD because we don't work at the moment with psychiatric hospitals. From the literature on blue enriched light as a treatment for SAD, compared to standard white light, it is difficult to find a consensus. In a polar work environment some people don't like it in my experience. We carried out long-term light supplementation at Halley (75°S) using bright, standard white light, compared to blue enriched light, initially 10,000K and the following year 17,000K (Philips Lighting). We looked at circadian phase, sleep and 'alertness' in winter, increasing the personal light exposure from the maximum of 500 lux, which was the most anybody previously saw on base in the winter. If you raise the light intensity such that people experience 2,000 lux maximum at some point during the day it makes a big difference. We get a circadian advance using 6-sulphatoxymelatonin as a marker and much improved sleep from the point of timing and from the point of view of efficiency. But we found very little difference between the standard, bright white and blue enriched light, the exposures in lux being approximately equivalent.[137] So I would say that it was not worthwhile yet choosing blue enriched light until we know a lot more.[138]

Rosenthal: Just a couple of points. With Dan Oren in our group, we did a study of red versus green light in the 1990s. We found that green was better than red for SAD, which is as one would expect even using just the conventional

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[134] Brainard *et al.* (2001); Thapan, Arendt and Skene (2001).

[135] See, for example, Lockley, Brainard and Czeisler (2003); Revell *et al.* (2005); Lockley *et al.* (2006); Revell *et al.* (2006).

[136] Professor Josephine Arendt added: '….[and] with Derk-Jan Dijk and co-workers to look at office workers (Viola *et al.* (2008)), with myself, Benita Middleton and Antarctic base doctors to optimize lighting for sleep and circadian phase on an Antarctic base (Francis *et al.* (2008); Mottram *et al.* (2011); Arendt (2012)).' Note on draft transcript, 29 January 2014.

[137] Mottram *et al.* (2011).

[138] Professor Josephine Arendt added: ' … or indeed green light which is also in contention…There is however some evidence that monochromatic blue or green light can be effective with much lower exposures than standard white.' Note on draft transcript, 29 January 2014.

photoreceptors.[139] That's the one point that I'd like to make. The other is that we did look at a polymorphism of a gene involved in melanopsin and found that in our SAD patients there were significantly more of a certain variant of that polymorphism than in healthy controls.[140] However, it only explained five per cent of the SAD patients, so that raises the possibility, or probability, that SAD may be multiply determined by many different genes that influence the circuitry between the retina and the brain. There must be many junctures, many neurotransmitters, many receptors, any of which might be important in that process. I also wanted to comment on the 'not just one receptor' that Rob raised.[141] Dan Oren and a colleague have just published in the *American Journal of Psychiatry* a paper wittily titled 'SAD and the not-so-single photoreceptors', which talks about different possible mechanisms whereby light might be working other than melanopsin, including an ingenious possible humoral mechanism involving some kind of portal system that Oren has been looking into.[142] And it's very ingenious, I hope it's correct. But anyway that's a nice article for people to be aware of. The point that I wanted to follow up with what Rob had mentioned earlier is that – and I think if I'm quoting you correctly – you had said that you're not all that surprised that the NICE group didn't conclude that light is effective given the multiplicity of different interventions.[143] Is that correct?

Lucas: No, no, I guess what I meant to get across is that one way that you could explain their decision is not their doubt that light is effective, but how would you define an effective treatment? That's what I was getting at. This comes really to talk a bit about what you were talking of, Jo, about your blue enriched light, and at some point you have to talk about light in quantitative not qualitative methods.

Rosenthal: Well, I think you could say, and I've looked at this to try and come up with a sort of standard recommendation that would encompass most of these studies, that they're white light by-and-large, almost all of them. They have light boxes or light fixtures that are about a foot square in terms of their illuminated surfaces, and size is very important in terms of the surface area that the light is

[139] Oren *et al.* (1991).

[140] Roecklein *et al.* (2009).

[141] See page 52.

[142] Oren, Koziorowski and Desan (2013).

[143] See page 48.

coming from, not just the fact that you can measure 10,000 lux at one point because nobody's sitting just at one spot without moving their head around. So the bigger the surface the more forgiving it is of people's moving around, which they will normally do. So I've said one foot square, white light between 2,500 and 10,000 lux and that's what most controlled studies that have had positive effects have found. I think that it's important to recognize the common thread between these studies, and not to say: 'Well, because they all differ from one another by small degrees here or there, you have to chuck out the entire canon of literature on the thing.' In terms of blue light, it's been marketed especially because of the melanopsin tie-in, but to Jo's point, there is actually no good evidence that it's any better than white light and there are no good efficacy studies out there indicating that blue light is the thing to use. There's also a blue light toxicity literature that people as distinguished as retinal expert, Dr Charlotte Remé in Switzerland, have expressed a lot of concern about.[144] Also, the French equivalent of the Food and Drug Administration has actually expressed concern even about white light LEDs being the light source of choice in indoor environments because of the amount of blue light emanating from those LEDs.

Follett: I gain the impression that over the years we've all carried out a number of experiments and there is no magic bullet. White light is about as good as you can get and there may be some additive if not synergistic effects by adding some other pharmacological agents.

What I'd like to turn to, if I could, is the last question: What status have these therapies in terms of clinical diagnosis, psychiatric practice, health insurance etc? So can we now go backwards, not to what the position is now, but what, over the 20 years since all this was first uncovered, has been the response of (a) the psychiatric profession and (b) of the major drivers on providing facilities and drugs? Is it a good story or less than good?

Lewy: This is something I would like Norm to comment on. He has a lot of information on this. There was a lot of resistance in the early days to recognize SAD as a disorder and insurance companies would not reimburse for a light fixture.

Follett: Are we talking 25 years ago?

Lewy: Yes, in the 1980s. But over the years, in my experience, insurance companies, with a letter from the physician, will reimburse about 50 per cent of

[144] See, for example, Grimm and Remé (2013); Ebert *et al.* (2012).

the cost of a light fixture. And it is cost effective when you consider how much a prescription for antidepressants would be for five months, year after year. And a light fixture lasts a long time.

Follett: Roughly how much does one of these one foot square light boxes cost?

Barksfield: £150.

Follett: Good Lord, that wouldn't pay for your average medic in this country for an hour.

Rosenthal: I think that you make the point brilliantly. It's such a small cost and it's a one-off cost and it helps people every single day through the winter months. It's ridiculous that it's not reimbursed. In America I would say a significant percentage, though a minority, succeed in getting insurance, and in my book I have included a sample letter to the insurance company to help providers help their patients get insurance reimbursement (Figure 13).

But I just want to flag what I thought was a brilliant comment that you made that we have to find an MP with SAD.[145] It reminds me of the old joke about when a secretary was being hired and some very ill-qualified candidate was selected and somebody said: 'Why did you select her?' And the personnel manager said: 'She's the boss' niece.' And that's really how business gets done unfortunately. I think that somebody who has the ear of law makers or policy makers is what is needed here because science hasn't done it, clinicians haven't done it, writing books hasn't done it. I think other mechanisms need to be invoked in order to get help for the millions of people who are suffering grievously from this condition. That's why I'm so grateful for this symposium and anything that it does to further the help for those people who are not being treated and not getting light, not getting what can make them function all year round.

Follett: One of the other great ways that pressure could be applied is, of course, if the funding agencies support research in this field very strongly. They have a great impact because they have access to government. Historically, how has the NIMH or the NIH looked at grants? How have the MRC and the Wellcome Trust looked at funding? You must have a sense historically what's happened?

Rosenthal: In the United States there's an intramural programme that's a concentrated programme in Bethesda, Maryland, where Al and I and Tom Wehr

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[145] See the comment by Professor Sir Brian Follett on page 28.

Sample Letter for Insurance Reimbursement

To Whom It May Concern:

This is to certify that Ms. Jane Smith has been a patient of mine since _____. I have treated her for recurrent major depressions (DSM-IV-TR 296.3), with a seasonal pattern. This condition, also known as seasonal affective disorder (SAD), has been shown in many studies in the United States and elsewhere in the world to respond to treatment with bright environmental light (light therapy). Light therapy is no longer considered experimental but is a mainstream type of psychiatric treatment, as evidenced by its inclusion in the authoritative *Treatments of Psychiatric Disorders, Third Edition,* a publication of American Psychiatric Publishing.[1] The effectiveness of light therapy was further confirmed in a 2005 meta-analysis published in the prestigious *American Journal of Psychiatry.*[2] To administer light therapy adequately, a light box, such as the one named in the attached invoice, is required.

Although a light box is an expensive piece of equipment, the experience of clinicians who have used it for many patients indicates that it saves a great deal of money over time by reducing the number of doctors' visits and the costs of medications and laboratory investigations of persistent symptoms, as well as the indirect costs of lost productivity. I maintain that in Ms. Smith's case, the use of such a light fixture should be regarded not only as a medical necessity, to be used in preference to, or in addition to, other forms of treatment, but also as a means of reducing her overall medical costs.

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[1]Oren, D. A., & Rosenthal, N. E. (2001). Light therapy. In G. O. Gabbard (Ed.), *Treatments of psychiatric disorders* (3rd ed., Vol. 2, pp. 1295–1306). Washington, DC: American Psychiatric Publishing.

[2]Golden, R. N., Gaynes, B. N., Ekstrom, R. D., Hamer, R. M., Jacobsen, F. M., Suppes, T., et al. (2005). The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. *American Journal of Psychiatry, 162*(4), 656–662.

Figure 13: Sample letter for insurance reimbursment.[146]

[146] Rosenthal (2013), page 152.

and Fred Goodwin did our work. There was a golden age where we were very well funded. Al can tell you about the extramural programme of the NIMH.

Follett: I hear it from every clinician from across the Atlantic.

Rosenthal: There was a golden age and it's passed. But I think that currently funding for light therapy and SAD research is probably very attenuated from where it was in its hey-day. I can't comment about the UK.

Follett: Let me ask you a bit further. Is it that money historically has come out of this area and gone into other areas of psychiatry or is the whole of psychiatric research underfunded? I can conceive of a situation where historically, with the rise of molecular biology and all the positives it brings, in some ways quite large areas have been squeezed out of the funding model. We've certainly seen it here.

Rosenthal: The pie has gotten smaller. It's much harder to get funded for anything in some areas, including psychiatry, seven per cent of grant applications get funded. It's very discouraging; you would know better than me, Al.

Follett: Does that suggest, Al, therefore that historically many clock biologists have not been drawn into this area of science?

Lewy: Governmental funding is just one leg of the funding stool. Another major leg is funding by pharmaceutical companies. However, it is difficult to patent light, although one of our colleagues has a light patent, and so you can't interest industry in supporting this work. So I'm just actually amazed that it's gotten this far without industrial support. It did have a golden age at the NIMH when Fred Goodwin went on to become the director.[147] After he left, the succeeding directors, for whatever reason, have focused on other areas. And hopefully both intramural and extramural funds will once again be directed more to this research, because there are so many important things for us to figure out. In the example of circadian misalignment, we don't know which rhythm (or rhythms) represented by the DLMO is misaligned with what other rhythm (or rhythms) related to the sleep-wake cycle that is actually causing SAD, or at least this component of SAD, and which needs to be corrected to treat SAD. Gerald Lincoln might have some ideas about thyroid hormone because it is so important in his work. Cortisol, the stress hormone, has a circadian rhythm, and I would think that's a likely candidate. I don't think it's melatonin. I want to be very clear that the melatonin rhythm is an important marker and dependent variable, and although you can give exogenous melatonin, especially in low doses, to shift

[147] Professor Frederick Goodwin was Director of the NIMH from 1992 to 1994.

the body clock (so that it can be an independent variable), the jury is out as to whether or not endogenous melatonin has an important function.[148] In any event, I don't think that the light is acting as an antidepressant by affecting the endogenous melatonin rhythm *per se*.

Arendt: You can live without melatonin, you can sleep without melatonin – but you sleep better with it. In general I agree with you.[149] But what I would like to say is that the Dutch group working with Serge Daan have looked at the intrinsic circadian period of SAD patients and of normals and they found that the SADs were no different from the normals in the various rhythms that they looked at, except for a reduction in the amplitude of the core temperature rhythm.[150] So I'd really like to hear your comment on that.

Follett: To those of you outside this scientific argument, might I explain? The group led by Serge Daan – one of the cleverest clock biologists alive – has discovered that the internal circadian system of SAD patients appears to be the same as normal patients. That may still be okay because it isn't actually what your internal clock may express, it's where it's located relative to the light-dark cycle, which historically appears to be at least Al's basic hypothesis on what he's changing when he gives either an early morning light pulse or a late afternoon melatonin pulse.

Lewy: I agree with your explanation; that's a reasonable explanation to understand the realm of possibilities here. The study by the Dutch workers, I think they studied seven patients.[151] They averaged their data and compared it to the average of normal controls, so if there was a phase-advanced subgroup in the patients, this would have brought the average of the SAD patients closer to that of the controls. You would really have to look and see if there was

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[148] Professor Lewy added: 'I have, however, proposed a few ideas over the years for possible functions of endogenous melatonin in humans (Lewy (1983a); Lewy *et al.* (1994); Lewy *et al.* (1992); Lewy (2007); Lewy (2013)).' Note on draft transcript, 14 February 2014.

[149] Professor Josephine Arendt wrote: 'Perhaps I should specify pineal melatonin. Treatment with quite large amounts to increase duration (supraphysiological) does not, in my experience, lead to depression (Arendt *et al.* (1984)). In general I agree with you. However, when it is correctly phased I think it reinforces what has been called "darkness physiology". To me its primary function is to convey information about daylength and it has modulatory effects with respect to the circadian system.' Note on draft transcript, 29 January 2014.

[150] Koorengevel *et al.* (2002). The paper is from Daan's group but he is not a co-author.

[151] Koorengevel *et al.* (2002).

this subgroup, as we have found in our studies.[152] So that's how I've always understood the Dutch study. It's a very difficult study to do, and I don't believe it's been attempted since it was published 12 years ago.[153]

Follett: Gerald, where do you come in from the point of view of 'seasonality'?

Lincoln: I think we should be able to learn lessons from what we've discovered in the last ten years about the basic mechanisms operating in the pituitary and hypothalamus that govern seasonal timing. It seems that the photoperiod transduction pathway involving melatonin is a separate system, distinct from the core timing process that goes on in the brain and peripheral tissues to regulate seasonality. Many organisms are non-photoperiodic and yet express robust circannual rhythms. The neuroendocrine and anatomical interface where endogenous timing and photoperiod control comes together is really key to our understanding. Long-term time keeping appears to be based on changes in the availability of thyroid hormones, critical in the control of cell biology, and governed by deiodinase genes activating locally in the hypothalamus.

This is timed by the way in which the melatonin signal that encodes photoperiod regulates thyroid-stimulating hormone (TSH) production from the pituitary gland. Unexpectedly, and in a most remarkable way, the TSH doesn't act peripherally, as for the normal control of the thyroid gland, but acts locally within the adjacent hypothalamus to alter the deiodinase gene systems and hence seasonal biology. One gene (*Dio2*) up-regulates and one (*Dio3*) down-regulates thyroid hormone availability – shifting the physiological and behavioural state from negative to positive or vice versa, driving the seasonal cycle.

Subjective Summer is the time when thyroid hormone biological activity is maximal, and on come all the proactive cellular mechanisms of neurogenesis, growth, replacement of tissue – it's like a 'metamorphosis'. There are remarkable parallels with frog metamorphosis. The change from tadpole to adult is also dependent on the local production of active thyroid hormones in the tissues where the transformations in cell biology actually happen. So here we have evidence that every summer seasonal mammals go into a high thyroid hormone state in the brain with a major impact on physiology and behaviour. In the

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[152] Lewy *et al.* (1987a); Lewy *et al.* (2006).

[153] Professor Alfred Lewy wrote: 'Also, related to what Brian has pointed out, there need not be a normative difference between patients and controls, as long as patients are different when depressed compared to when they are euthymic, an ipsative difference (Lewy *et al.* (1987b)).' Note on draft transcript, 14 February 2014.

Figure 14: Dr Thomas Dixon

winter, the systems are globally shut down for the very logical reason – to conserve energy. So here is a helpful hint as to the fundamental nature of the control of seasonal transitions that may underlie the rhythmicity of SAD.[154]

Dixon: I'm afraid it doesn't really follow on exactly from what we just heard but for me this is such a fascinating symposium; to hear about this incredibly complex and imaginative and lengthy process that the scientists, clinicians, and patients have all been involved in, which for me is like this incredible case of how do you create a disorder? You've got to put it a particular way. How do you create a belief in a real disorder that scientists and doctors and patients and the general public and journalists believe in and recognize and can all talk about? And that's what we've been hearing, this amazing sort of sociology of medicine, in a way, in practice over the last 30 years and it's incredibly complicated. It's about animal behaviour; it's about circadian rhythms; it's also about the thing that Professor Rosenthal became very passionate about –suffering; it's about real human beings having real suffering and frustrations of trying to create knowledge and treatment around that. So that's just a comment that it has been really fascinating for me to hear all about this. I wanted to ask a question which was more about how the social and cultural history of this, you might say, has played out over the last 30 years. I've become aware of SAD during my lifetime,

[154] See Hazlerigg and Loudon (2008); Hazlerigg and Lincoln (2011); Stevenson and Prendergast (2013).

probably 15 years ago. I started hearing friends say that they had SAD. These people kind of self-diagnosed so it's an amazing achievement. Around the world people are self-diagnosing themselves with this condition. It doesn't happen very often. And obviously we have experts here who run a patients' association in this country. So I wanted to ask about the social and cultural history of it: Are there still a thousand people a day contacting SADA or has it kind of passed its peak in terms of something that's created a great deal of public recognition?

Eastwood: I confess that I've taken a back seat in SADA for the last 10 years and I've only just become involved again. We had 15 intensive years of non-stop work and media interest, and there was a point at which I felt that every taxi driver in London knew all about SAD, the mechanism, how it was treated, and pretty well everybody said: 'Oh I know how that feels', but they don't. It was easier to get through to the media and make SAD generally known about than get the medical profession to take an interest. It still is, I think.

I take some of the blame for this on behalf of SADA. In the early days, we tried to get enough good psychiatrists to run clinics in tertiary care in all areas of the UK and not just the two London ones. Some SADA members went to their local psychiatrist and, by the time they'd interested them in SAD, they were often prepared to see more patients. It was almost socially engineered in a way; we had our own tame psychiatrists that we could rely on to test, diagnose, and treat SAD so maybe it is not surprising that too few medics know much about it.[155]

There's something about SAD that just seems to be sad! I know that sounds meaningless in the scientific sense but, of all the hundreds of thousands of people I've heard from over the years, I can identify with almost all of them. The severity, of course, differs and, as we already said, the demographic aspect of SAD; someone like Norman can feel great in South Africa, not so good in New York, fine in Florida, but he'll get worse if he comes here to the UK. He has definitely got whatever it is that causes SAD, but it varies wherever he goes on the planet and the same applies to me and probably millions of others. That's fine if it's mild enough that you can just adjust as with jet lag or other circadian rhythm disorders, but it doesn't explain the really bad cases.

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[155] Ms Jennifer Eastwood wrote: 'I think that when SADA started and its members met other sufferers for the first time, we felt that we had been so traumatized by medical idiocy in the past that we wanted to take control of the situation and get as many sufferers properly diagnosed and treated.' Note on draft transcript, 31 January 2014.

There's just one thing that I think Norm mentioned and Chris Thompson published some research on, that I'd like to ask about, that is, sub-sensitivity or super-sensitivity to light.[156] I feel, increasingly, as I get older, that what ambient light there is doesn't get through to my hypothalamus. Maybe that is because for years I've been pumping hundreds of thousands of lux through my eyes so if I'm in somewhere semi-dark, light doesn't really get through. Another query is why a lot of us fall asleep in front of our light boxes when bright light is supposed to keep us awake. Many of us probably have some form of sleep disorder, mainly Sleep Phase Delay, and realise that we were all mostly all night owls before we started to have SAD.[157]

The difficulty is that once Professors Checkley and Thompson went and Dr John Eagles from Aberdeen and others retired, specialist SAD research and treatment seem to have disappeared in the UK. SADA was able to generate a lot of media interest but I sometimes wonder if it meant that the medics and scientific people thought: 'Look at these awful people going on about this in the popular media, even *The Sun*', and they didn't approve. Maybe they switched off and decided that SAD wasn't a proper illness, just a late twentieth-century fad, so they didn't take it seriously. After all, you can buy a light box for a hundred quid, use it till you feel better, maybe tell your GP about it. Some people don't even tell their GPs that they have SAD or a milder version of it.[158]

Hanson: I just wanted to add a little bit to that to answer the original question. There were certainly bucket loads of enquiries to start with, weren't there? And I think what we have now is exactly what you'd expect – a constant trickle of newcomers. Obviously we've got our core membership but we don't get a huge influx like there used to be at the beginning. I think there are a lot of people who had been living with it for a long time and they all surfaced when SADA started. Now things have settled down and we are getting a steady stream of the next generation. The other point I wanted to make was that I think

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[156] See, for example, Thompson, Stinson and Smith (1990). This paper reports evidence of super-sensitivity to light in the winter and sub-sensitivity in the summer.

[157] Ms Jennifer Eastwood added: 'Incidentally, while on the subject of sleep, I was once contacted by a Scottish lady who had had her pineal gland removed during brain surgery (the surgeon thought she didn't need it!) and she could hardly sleep at all after that. I don't know what became of her but I expect she died through lack of sleep.' Note on draft transcript, 31 January 2014.

[158] Ms Jennifer Eastwood wrote: 'We need scientists like the circadian rhythm researchers to continue the work that began in the 1980s to take our knowledge further and enable us to understand more about this horrendous illness.' Note on draft transcript, 31 January 2014.

Figure 15: Professor Alfred Lewy, Ms Carol Barksfield, Ms Jennifer Eastwood, and Ms Helen Hanson

we've touched a nerve with the public and the press precisely because SAD is a continuum. Jennifer made the point that she was always being accosted by people who said that they'd got it and she said that they hadn't. The thing is most human beings have it to a small extent, some people are a bit further along the spectrum, and then there are people like Jennifer, who are seriously affected. But that's the thing that's touched the public, I think. It's something that they can all understand to a certain degree.

Follett: Winter blues.

Hanson: Yes, that's why the press love it. I sometimes feel that the press are actually much more cooperative than the medical profession.

Follett: Well, that would not be a difficult step to have achieved.

Lewy: Just to follow up on some of the things that you two have talked about: I don't think the light box market is saturated. The treatment of choice is well known, and there still is a steady demand for buying light boxes in the USA.

Follett: What's the market on eBay?

Lewy: Good question. I usually get several media requests to do interviews every winter, and it actually surprises me because you would think this would be old news. But I think the American public's memory for recent news is less than 365 days or something [laughter], maybe 200 days. And every winter there

are reporters who say: 'Oh boy, this would be a great story to write about' and it usually occurs on some rainy, cloudy, or cold day; that's what precipitates it. And I have to tell them, you know, there are many climactic and other changes that occur across the seasons: allergies, allergens, humidity, temperature, but SAD is specifically related to day length and I go into the phase shift hypothesis with the later sunrise being most consequential for most people. One other thing, because Jennifer mentioned light sensitivity tests: after we showed the light could suppress melatonin, in 1981 we published a small study in *The Lancet* (Tom Wehr and Fred Goodwin were co-authors) on four bipolar patients, who were either manic or depressed, and showed that they suppressed their melatonin twice the extent as did normal controls.[159] This was followed up with John Nurnberger showing that euthymic bipolar patients, that is patients who were neither manic nor depressed at the time, were super-sensitive to light using the melatonin suppression test.[160] And John Nurnberger followed that up with at least one other study.[161] But for some reason, there hasn't been a lot of activity in this area. Whether SAD patients are either super-sensitive or sub-sensitive to light, maybe Rob would like to comment. It's hard to do these studies. The pupil accommodates to the light intensity so George Brainard was one of the people who dilated the pupils to make that constant, and there are other factors, which makes it a messy sort of test. I don't think we really know whether SAD patients are super- or sub-sensitive to light. It's a good area for future research.

Rosenthal: When I told you the other effects of light therapy, namely for PMS and bulimia, there's a young Dutch researcher, Ritsaert Lieverse, who did a brilliant study published in the *Archives of General Psychiatry* on the use of bright light for non-seasonal depression in the elderly, and it was strongly positive.[162] It was a wonderful, really definitive study showing that light can be helpful for depression in general. Dr Dixon raised a couple of points: how does one construct a syndrome or a condition in the absence of a definitive marker, which is the case for all psychiatric syndromes. The classic paper was by John Feighner. It was published in the 1970s. He came from the St Louis group and they set out a series of criteria by which you could define a condition: it had to be distinct from other conditions, the demographics had to fall into a certain

[159] Lewy *et al.* (1981).

[160] Lewy *et al.* (1985).

[161] Nurnberger *et al.* (2000).

[162] Lieverse *et al.* (2011).

Figure 16: Professor Norman Rosenthal, Professor Rob Lucas, and Professor Alfred Lewy

pattern, family history was a feature, clinical profile, as was course in terms of its natural history, response to treatment.[163] And when all of these clustered around certain common elements then there was reason to regard the entity in question as a syndrome. There were different kinds of validity based on those various factors. Bob Spitzer does a very good paper in the book that I co-edited with Mary Blehar from the proceedings of the first symposium of SAD, following the Feighner criteria.[164] For SAD there's a common demographic profile: it is three times as common in women as in men; in women it starts more commonly after the menarche, so female sex hormones appear to be relevant. There is an atypical vegetative pattern of depressive symptoms in terms of oversleeping, overeating, carbohydrate craving, weight gain, and fatigue. These symptoms all appear to go together – evidence for concurrent validity. Obviously, the course is distinctive in terms of its seasonal variation. The response is distinctive in terms of the syndrome's distinct sensitivity to light. There are all the variables that Feighner laid out to say that SAD is, and should be, a distinct condition. I should mention that there are many seasonal influences other than winter. Suicides peak not in the winter, but in the spring and summer. And this occurs both in the northern and southern hemispheres. There is a distinct form of

[163] This led to the use of the 'Feighner criteria' in psychiatry research which, along with the Research Diagnostic Criteria, were central to the development of *DSM-III*. See Feighner *et al.* (1972).

[164] Spitzer and Williams (1989).

summer depression that has opposite vegetative symptoms to the winter depression (decreased sleep, loss of appetite and weight, and agitation) and it's well known that suicide is more likely to occur when depression coexists with activation and agitation, as opposed to being slowed down and retarded. The latter is the case in winter depression and the former (agitation and activation) in summer depression. So suicides are more common in the summer.

In terms of light sensitivity, electroretinogram studies by Marc Hébert and others,[165] electrooculogram studies, in addition to the work that I mentioned on photoperiodism by Tom Wehr and myself, all suggest that people with SAD are sub-sensitive to light, which would explain why they need more light, in some cases much more light. For example, some people may need more than one light box at certain times.

Now, why has the media lost interest? Well, the first thing is, it's old news. The media likes new news, not old news. And so from their point of view it's a twice-told tale, or more what they call a soft media story. So they'll show interest in the subject but the story can easily get bumped by something more important that comes along. The other thing that they do is they put you in cold storage. So I might be walking around the neighbourhood and somebody says: 'Oh you were on television this morning.' They schlep the story out of moth balls and put it back on the TV again without the expert even knowing. If the folks from SADA are wondering why you aren't getting all the enquiries you used to get, think of what's happened since the description of SAD – the internet. There was no significant internet back in the early 1980s. Now if you Google 'Seasonal Affective Disorder' you'll get millions of hits. So anybody who wants help can go on the internet, find out the light companies, order their lights, and be done with it. And that's wonderful because people should be able to get help easily.

The last point that I would just like to mention is the question of whether evening light added to morning light is useful. Many patients with SAD, in my experience, use both evening and morning light therapy. I wonder about the experience of the good folks from SADA in this regard. Do you need a little light therapy pick-me-up in the afternoon, or you'd otherwise feel wilted?

Eastwood: The use of afternoon light is certainly encouraged, mainly because a lot of people don't have time to use enough light therapy before going to work or school so have to top up in the evening, but as early as possible so that they

[165] See, for example, Hébert *et al.* (2004).

can get to sleep at night. I'm retired now so I spend every morning glued to a big light box. You know that you have to just push this light through to your brain, it's as simple as that.

Lewy: As long as it's not too late in the evening and causing a phase delay[166] I'm fine with topping up any time in the middle of the day or late in the afternoon, even early evening, but not late in the evening (after 7 or 8pm) because that's when you're going to get a phase delay.[167] I'd just like to add one thing about the seasonal pattern that Norman described. He's absolutely correct, and it's interesting that the incidents of suicide peak in the autumn, with another peak in the spring. But these are not – correct me if I'm wrong, Norm – regular seasonal cyclers who get depressed at the same season of the year, every year. These are cross-sectional, epidemiological of mostly non-seasonal depressives. These are not people who get depressed year after year after year.

Rosenthal: No, it's a complex issue. Some researchers have found autumn and spring peaks in suicide. Most people are finding the late spring and summer to be the peak time for suicide and this applies in both northern and southern hemispheres. Al is right in that the spring people, the ones who just get depressed in the spring, that's not a regular pattern, but the summer people regularly get depressed summer after summer and it's really sad because you can't give them the relatively easy answers that are available to the winter folks.

Lucas: I just wanted to come back to the question we were talking about earlier, about how it's perceived both by the general public and by the scientific establishment. It may be my personal experience in the UK scientific establishment that the term 'Seasonal Affective Disorder', which I think is a beautiful term to have coined because it's so descriptive of the condition, is regarded as kind of 'new agey' by some in the UK scientific establishment and that we suffer a little bit from that. And that may be also why the media regard it in a particular way. So the key feature of SAD, from a biological perspective,

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[166] Lewy, Sack and Singer (1984, 1985).

[167] Professor Lewy wrote: 'As I mentioned earlier, there is a smaller subgroup who should get bright light in the evening and avoid it in the morning, but in either case bright light should not be given at both times. A similar principle applies to treating free-running blind people with melatonin (Sack, Stevenson and Lewy (1990); Sack *et al.* (2000); Lockley *et al.* (2000)) so that when they entrain they do so at the normal phase (such that their endogenous melatonin onset occurs 2–3 hours before desired sleep onset); accordingly, most of them (who have endogenous periods greater than 24 hours) should take melatonin about 6pm (Lewy *et al.* (2004)), but a few of them (who have endogenous periods shorter than 24 hours) should take melatonin at waketime (Emens *et al.* (2006)).' Note on draft transcript, 14 February 2014.

seems to be that it's treatable by light, so I was wondering whether if it was called 'light responsive affective disorder' that might help us out in some ways. And, as a counter factual thought experiment, if it was called 'light responsive affective disorder', how that would change the way that the world in general viewed this important condition?

Eastwood: If you call it light responsive, you're almost putting the cart before the horse because, though you and I know that the original guys at NIMH have sorted it, you tell that to NICE or the British establishment and they will say: 'Any bunch of Yanks can come up with a new condition, they've got more money for research than anybody else.' Nobody has really proved it as light responsive in the UK to the satisfaction of the medical establishment. I completely agree that light is the fundamental element involved in SAD, but we can't leave out drugs because they are the only treatment recognized by NICE, other than cognitive behavioural therapy of course.[168] SADA has always done its best to present SAD to the media as respectably and positively as possible. We were very careful about who appeared on TV and radio on behalf of SADA; they had to be articulate and professional so as not to reinforce the stereotype of mental illness. I think that helped us to attract a lot of media attention. But I feel that it has only got us so far.

Lucas: Is there a country where it was called something else?

Lewy: We call it winter depression almost as often as Seasonal Affective Disorder, but as Norm pointed out there's a very tiny group of people that get depressed in the summer on a regular basis. The original theory for the summer depressives, maybe Norm would like to go into that, had to do with temperature and humidity. But in Portland, I urge you to go there in the summer, we have little humidity, it doesn't get very hot and yet we have some summer depressives. I've been using low-dose melatonin in the afternoon/evening with them to counteract the longer day with the chemical dark signal, melatonin, because I think that both annually recurrent winter and summer depression are related to circadian misalignment.[169] One occurs with the shorter days, the other occurs with the longer days.

Rosenthal: One of the big themes in today's whole discussion has been the difficulty getting this entity accepted, and as anybody who has any product, process, or brand name will tell you, the last thing that you want to do is change

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[168] See pages 44–5 and note 109.

[169] Lewy (2013).

Figure 17: Participants at the Witness Seminar

your name because you'll then sow confusion among people who are already unaccepting and confused. So, even if we were to assume that your suggestion is the far better name, and Jen has contested that, you really want to be very careful about mixing people up, as can easily happen.

Lucas: I'm not suggesting it.

Arendt: I think SAD is a wonderful name but I think Rob is right, that it is seen as slightly alternative. A couple of days ago, I went to something called the Shuffle Festival, which is in a disused psychiatric hospital in the Mile End Road. It's run by Danny Boyle's daughter, Grace Boyle, and it featured winter depression and a light treatment room among all sorts of other things.[170]

Follett: Let me draw it together. First of all I'd like to thank everybody for coming and particularly our colleagues who have come over the Atlantic to these northern latitudes on December 10th, so close to the winter solstice. Also, of course, Queen Mary and the Wellcome Trust who've put all this on. I leave it

[170] The first Shuffle Festival, an initiative of the East London Community Land Trust, exploring artistic talent in London's East End, was held in August 2013 at St Clement's Hospital, a former workhouse and psychiatric hospital in Mile End. A Winter Shuffle was held in December 2013. See the Shuffle website at www.shufflefestival.com (visited 3 June 2014), and the filmed recording of the lecture given by Professor Jo Arendt, 'Light, Dark and living in Antarctica', at www.youtube.com/watch?v=vMGgbtkoYN4 (visited 3 June 2014). Danny Boyle (b. 1956) is a film director, producer, and writer.

with one observation – it's really Rob's point: there is a treatment and it appears to work. It's not actually a difficult treatment, it may not be entirely pleasant but nevertheless it is straightforward and it is not regulated by the NHS. So isn't the answer 'get the message out'. It would be good if NICE agreed that half the price or so of a light box was paid by the taxpayer, but the cost of around £150 is not that great. So I'm optimistic on the treatment front but much less so on our ability to understand the underlying physiology. Frankly it is going to be impossible to solicit millions of dollars to unravel this problem. We do not have a good animal model to understand how daylight-length affects 'mood'. And therefore I come away from it feeling, why haven't we got billboards advertising it?

Tansey: May I add my thanks and the thanks of my team to you all for coming and being so frank, opening up so many questions and issues. I'm very conscious we haven't even addressed some of them. I do apologize about the timing: we did realise that a December afternoon was not ideal for this meeting but we want to try and get something out for next year because it is the 30th anniversary of the very first SAD paper and Thomas Dixon and I have an idea that we'd like to have a press campaign for 'SAD at 30' or something like that. And, finally, I do want to thank our excellent chairman. Thank you so much, Brian.

Appendix 1

Regulations with which light boxes need to comply[171]

Medical Directive 93/42/EC amended 2007/47/EC – Main Directive from Europe, which covers the regulation of Medical Devices. Light boxes are considered to be an invasive device under Annex IX, as they change the chemical balance in the brain

BS EN 60601-1:2006 – Medical electrical equipment Part 1: General requirements for safety

BS EN 60601-1-2:2007 – Medical electrical equipment Part 1–2: General requirements for safety – Collateral standard: Electromagnetic compatibility – Requirements and tests

BS EN 60601-2-57 – Medical electrical equipment. Particular requirements for the basic safety and essential performance of non-laser light source equipment intended for therapeutic, diagnostic monitoring, cosmetic/aesthetic use

BS EN 1031: 2008 – Information supplied by the manufacturer with medical devices. This covers what is to be put in the Instructions for Use

BS EN 980: 2008 – Graphical symbols for use in labelling of medical devices

BS EN ISO 14971:2009 Medical devices – Application of risk management to medical devices. Revised 2012

BS EN ISO 13485:2003 – Medical Devices Quality Management System. Revised 2012

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[171] Information supplied by Ms Carol Barksfield, who wrote: 'We have the light boxes tested to all the above standards and it is mandatory to comply with the overarching Medical Directive from Brussels, 93/42/EC. We were one of the first medical device companies and the first light box manufacturer to attain the Quality System, BS EN ISO 13485. This is not mandatory but we hold this as I thought that if we were manufacturing light boxes it was silly not to.' Email to Ms Caroline Overy, 8 April 2014. BS EN ISO 3485 is a key standard to measure the quality of medical equipment, medical instruments, and medical technology.

Appendix 2

The Seasonal Pattern Assessment Questionnaire[172]

The purpose of this form is to find out how your mood and behavior change over time. Please fill in all the relevant circles. Note: We are interested in *your* experience; *not that of others* you may have observed.

1. In the following questions, fill in circles for all applicable months. This may be a single month ●, a cluster of months, ●●●, or any other grouping.

   At what time of year do you . . .

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec		
A. Feel best	○	○	○	○	○	○	○	○	○	○	○	○	○	No particular months stand out as extreme on a regular basis
B. Tend to gain most weight	○	○	○	○	○	○	○	○	○	○	○	○	○	
C. Socialize most	○	○	○	○	○	○	○	○	○	○	○	○	○	
D. Sleep least	○	○	○	○	○	○	○	○	○	○	○	○	○	
E. Eat most	○	○	○	○	○	○	○	○	○	○	○	○	○	
F. Lose most weight	○	○	○	○	○	○	○	○	○	○	○	○	OR ○	
G. Socialize least	○	○	○	○	○	○	○	○	○	○	○	○	○	
H. Feel worst	○	○	○	○	○	○	○	○	○	○	○	○	○	
I. Eat least	○	○	○	○	○	○	○	○	○	○	○	○	○	
J. Sleep most	○	○	○	○	○	○	○	○	○	○	○	○	○	

2. To what degree do the following change *with the seasons?*

	(One circle only for each question.)				
	0	1	2	3	4
	No change	Slight change	Moderate change	Marked change	Extremely marked change
A. Sleep length	○	○	○	○	○
B. Social activity	○	○	○	○	○
C. Mood (overall feeling of well-being)	○	○	○	○	○
D. Weight	○	○	○	○	○
E. Appetite	○	○	○	○	○
F. Energy level	○	○	○	○	○

FIGURE 1. Questionnaire for evaluating your degree of seasonality.

Modified from the Seasonal Pattern Assessment Questionnaire (SPAQ) of N. E. Rosenthal, G. Bradt, and T. Wehr (public domain).

Note to scholars and researchers: Over the years, many people have written to me requesting permission to use this questionnaire. The SPAQ was developed under the aegis of the NIMH, a government institution, and is therefore in the public domain and can be used freely by scholars and researchers. Notifying its authors that you plan to use this instrument in a research project is merely a courtesy.

[172] This questionnaire is in the public domain and downloaded from www.guilford.com/add/forms/rosenthal2.pdf?viewpdf (visited 10 June 2014).

3. If you experience changes with the seasons, do you feel that these are a problem for you? ○ No ○ Yes

	Mild	Moderate	Marked	Severe	Disabling
If yes, is this problem	○	○	○	○	○

4. By how much does your weight fluctuate during the course of the year?
   - ○ 0–3 lbs.
   - ○ 4–7 lbs.
   - ○ 8–11 lbs.
   - ○ 12–15 lbs.
   - ○ 16–20 lbs.
   - ○ Over 20 lbs.

5. Approximately how many hours of each 24-hour day do you sleep during each season? (include naps)

		Hours slept per day	Over 18 hours
○	Winter (Dec 21–Mar 20)	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫ ⑬ ⑭ ⑮ ⑯ ⑰ ⑱	○
○	Spring (Mar 21–June 20)	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫ ⑬ ⑭ ⑮ ⑯ ⑰ ⑱	○
○	Summer (June 21–Sept 20)	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫ ⑬ ⑭ ⑮ ⑯ ⑰ ⑱	○
○	Fall (Sept 21–Dec 20)	⓪ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ⑩ ⑪ ⑫ ⑬ ⑭ ⑮ ⑯ ⑰ ⑱	○

6. Do you notice change in food preference during the different seasons? ○ No ○ Yes

   Please specify:

   _____

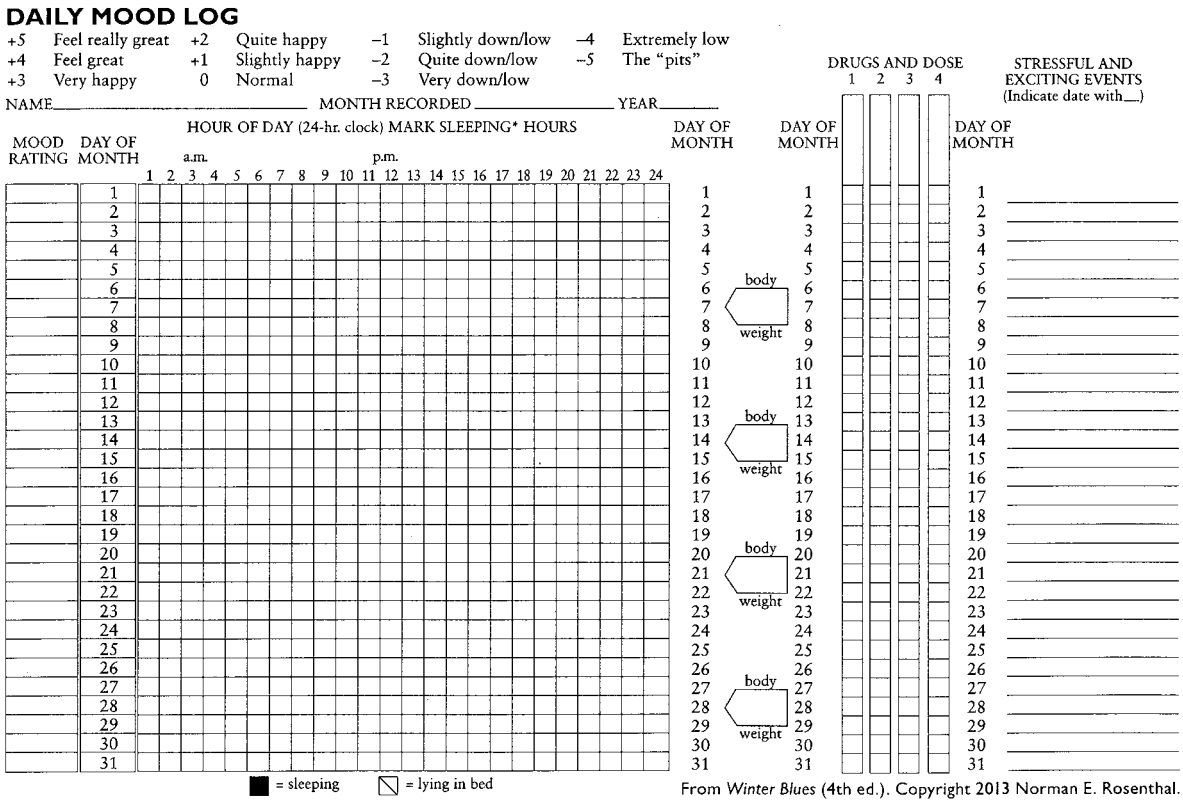
   _____

   _____

FIGURE 1 (*cont.*)

Appendix 3

Daily Mood Log[173]



DAILY MOOD LOG

+5 Feel really great +2 Quite happy –1 Slightly down/low –4 Extremely low
+4 Feel great +1 Slightly happy –2 Quite down/low –5 The "pits"
+3 Very happy 0 Normal –3 Very down/low

NAME_____ MONTH RECORDED _____ YEAR_____

MOOD RATING | DAY OF MONTH | HOUR OF DAY (24-hr. clock) MARK SLEEPING* HOURS (a.m. 1 2 3 4 5 6 7 8 9 10 11 12 p.m. 13 14 15 16 17 18 19 20 21 22 23 24)

DAY OF MONTH | body weight | DAY OF MONTH | DRUGS AND DOSE 1 2 3 4 | DAY OF MONTH | STRESSFUL AND EXCITING EVENTS (Indicate date with__)

■ = sleeping ▨ = lying in bed

[173] The Daily Mood Log is reproduced from Rosenthal N E. (2013) *Winter Blues,* 4th edn. New York: The Guilford Press, page 328. Copyright: Guilford Press. Reprinted with permission of The Guilford Press.

Biographical notes*

Professor Josephine Arendt

PhD, FRCPath, FRSM, Dr med h c (b. 1941) is Emeritus Professor of Endocrinology at the University of Surrey, Emeritus Director of the Centre for Chronobiology, and Director of Stockgrand Ltd, a company that she founded in 1988 to exploit expertise in light and melatonin. She is a founding member of the European Biological Rhythms Society (previously the European Pineal Society) and of the Society for Light Treatment and Biological Rhythms. She was President of The European Pineal Society (1987–1990), President of the Gordon Research Conference on Pineal Cell Biology (1998–2000) and has been awarded a number of medals (St Goran's Hospital, Karolinska Institute, Justus von Liebig University, Giessen, the Ernst and Berta Scharrer Medal, University of Frankfurt and the Kappers Medal of the European Biological Rhythms Society). She has served on a number of editorial boards, including Associate Editorship and currently has editorial board membership of the *Journal of Biological Rhythms*. She was an expert adviser to the IARC (WHO) group on the cancer risks of shift work, together with other committees related to melatonin, light, and chronobiology. She pioneered immunotechnology for the detection and measurement of melatonin and its metabolites, their circadian and seasonal response to light, and their use to characterize circadian responses, particularly in conditions such as jet lag and shift work. She first described the chronobiotic properties of melatonin in relation to sleep and the circadian system, and initiated its use for circadian rhythm-related sleep disorders, such as jet lag and non-24h sleep disorder of the blind. She highlighted the importance of light and melatonin in humans and continues to pursue research interests in this area, particularly in polar regions.

Ms Carol Barksfield

BA (b. 1954) studied Business Administration at Brunel University. She took over as Managing Director of SAD Lightbox Company in July 1996 and in 1998 successfully steered the company through the Medical Directive 93/42 to become the first

* Contributors are asked to supply details; other entries are compiled from conventional biographical sources.

light box company in the UK to achieve this certification. She has since guided it through the Medical Quality Standard ISO1348, again the first UK light box company to gain this qualification. Since taking over the company, the range of light boxes manufactured has evolved to embrace the latest designs and technology. The light boxes have been used in the Dana Centre, part of the Science Museum to promote public awareness of Seasonal Affective Disorder. All the light boxes are widely used in clinical trials, most recently by Outlook Southwest, UCL, and in clinical trials in Amsterdam and Madrid.

Professor Stuart Checkley

FRCPsych, FRCP, FKC (b. 1945) qualified in medicine at the University of Oxford in 1970, and after house appointments was a Registrar in Psychiatry at the London Hospital (1974–1976). In 1976 he moved to the Maudsley Hospital, London, where he where was Consultant Psychiatrist from 1981 to 2001. He was Dean at the Institute of Psychiatry, King's College London, from 1989 to 2001. He is currently a retired consultant psychiatrist at the Maudsley Hospital, and Emeritus Professor of Psychoneuroendocrinology.

Professor Philip Cowen

MD FRCPsych (b. 1951) trained in medicine at University College Hospital, London, and then in psychiatry at King's College Hospital, London. He went to Oxford to work in the MRC Unit of Clinical Pharmacology. Since 1983 he has been an MRC Clinical Scientist and Honorary Consultant Psychiatrist in the Department of Psychiatry in Oxford. He was elected to a personal chair in Psychopharmacology in the University of Oxford in 1997 and the Academy of Medical Sciences in 2001. His main interests are in the biochemistry and treatment of mood disorders, particularly the pharmacological management of resistant depression.

Professor Ilana Crome

MD FRCPsych (b. 1951) is Emeritus Professor of Addiction Psychiatry, Keele University and Honorary Consultant Psychiatrist, South Staffordshire and Shropshire Healthcare NHS Trust. She is Past President of the Alcohol and Drugs Section of the European Psychiatric Association, international editor of *American Journal of Addictions*, and on the International Advisory Boards of the *British Journal of Psychiatry*, *Addiction*, and *Journal of Psychopharmacology*. She was Chair of the Faculty of Substance Misuse (1998–2002), currently a co-opted

member of the Addictions Faculty, and founding member of the Academic Faculty (2005–2012) at the Royal College of Psychiatrists. She was a member of the Advisory Council on the Misuse of Drugs (ACMD) (2002–2010), and was Chair of the Treatment Working Group; she sat on the Executive of the Society for the Study of Addiction (1994–2011). She is a Trustee on the Independent Scientific Committee on Drugs and Vice-Chair of the Professors of Psychiatry Club. Her continuing research interests include addiction along the life course, and the enhancement of training and education in substance misuse in health professionals at all levels.

Dr Thomas Dixon

PhD (b. 1973) completed his PhD and held a British Academy Postdoctoral Fellowship at the University of Cambridge (2000–2003). He was a Lecturer in History at Lancaster University from 2004 until 2007, when he joined the School of History at QMUL. Since 2008 he has been Director of the Queen Mary Centre for the History of the Emotions. His current research interests are in the histories of emotions (especially tears and weeping), medicine and science, and in the cultural history of philosophy (including stoicism and existentialism). Previous research projects have explored the histories of psychological categories, Victorian moral thought, and the relationships between science and religion.

Ms Jennifer Eastwood

BA PGCE (b. 1952) graduated in French from the University of Newcastle in 1973 and moved with her husband to London to start her career, initially teaching, then in the Civil Service. Her aim was to become an arts administrator and in 1977 she was awarded funding by the Arts Council of Great Britain to set up the Early Music Network, a nationwide series of 100 concerts of music from the thirteenth to eighteenth centuries. She continued to run the series, along with other freelance activities in early music, music education, broadcasting, and writing, until 1983, when her health prevented her from continuing with creative and executive work. She undertook various part-time administrative jobs while struggling with her mental health and undergoing many operations for an unrelated physical condition. She started employment with Imperial College London in 1985 when her health problems were under control and spent the remainder of her working life there as support staff for several different research groups. In 1987 she set up the SAD Association to

raise awareness of SAD and ensure that sufferers were able to access treatment. Her interests include singing and getting away from the UK as often as possible.

Professor Sir Brian Follett

FRS PhD DSc (b. 1939) graduated in biological chemistry followed by a PhD in pharmacology. He held a series of academic posts in zoology/biology departments over the next 30 years in Washington State University, University of Leeds, University of Wales Bangor, and University of Bristol. His research focused upon seasonal breeding in birds and mammals and he was Director of the BBSRC Research Group on Photoperiodism and Reproduction. In all, about 420 papers emanated from the Group, with especial emphasis upon endocrinology, the neural pathways involved in controlling reproduction, and the biological clocks used to measure day length. This research was carried out on a range of birds (quail, starlings, albatrosses, ducks) and mammals (hamsters, sheep). He was elected to the Royal Society in 1984 and was later its Biological Secretary. In parallel, he had a growing administrative focus and was Head of Zoology in Bristol for 14 years before being appointed to the Vice-Chancellorship of the University of Warwick in 1992. Nationally he served on the council of AFRC, the UFC, and HEFCE. He has chaired government enquiries and reported on university libraries, JISC (for HEFCE), Creation of an Arts Research Council for the British Academy/ESRC, the Foot-and-Mouth Disease Outbreak of 2001, and the Alder Hey Children's Hospital scandal of 2001. After ending his stint at Warwick University he became Non-executive Chair of the Teacher Training Agency (2003–2009) and the Arts and Humanities Research Council (2001–2008). Since 2002 he has been a (visiting) Professor of Zoology at Oxford, where he lectures undergraduates. He has received various honours from UK and foreign universities.

Professor Frederick Goodwin

MD (b. 1936) received his MD from St Louis University School of Medicine in 1963 and joined the NIMH in 1965 where he was Scientific Director (1981–1988) and Director (1992–1994). Between 1988 and 1992 he was head of the Alcohol, Drug Abuse, and Mental Health Administration. In 1994, he was appointed Research Professor of Psychiatry and Director of the Center on Neuroscience, Medical Progress, and Society at the George Washington University Medical Center, becoming Clinical Professor

of Psychiatry in 2008. His research focuses on psychopharmacology, especially bipolar disorder, major depression, and suicide. He is the author of over 460 publications, including the textbook, *Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression* (with Kay Redfield Jamison), and from 1998 to 2005 he hosted the weekly public radio show, *The Infinite Mind* (guest host until 2007).

Ms Helen Hanson

BA (b. 1950) read French and Italian at Bedford College, University of London. She went into teaching, becoming Head of Modern Languages and Director of Personal and Social Education in a Kent comprehensive school. In 1990, following the success of her work as a printmaker, she left education to become a professional artist. She exhibited her etchings throughout the UK and abroad, was a member of Greenwich Printmakers, and a founder member of South Bank Printmakers. She has also been a member of the Society of Botanical Artists for many years and organizes *Florum*, a major annual exhibition. She was diagnosed with SAD in 1991 and helped as a volunteer in the early years of SADA, returning to join the committee in 2012. She has been Chairman since May 2013.

Professor Alfred Lewy

BS MD PhD (b. 1945) graduated in biochemistry from the University of Chicago in 1967 and obtained his MD and PhD in pharmacology in 1973. His PhD dissertation on operant behaviour and norepinephrine metabolism was published in *Science* in 1972. He was a house officer at Mt Zion Hospital between 1973 and 1975, finishing his residency in psychiatry at the National Institute of Mental Health (NIMH) in Bethesda MD. He was a Clinical Associate and then a Staff Psychiatrist at the NIMH until 1980, and then he was a Guest Worker at the National Eye Institute until his move to Oregon Health & Science University in 1981, where he became Director of the Sleep and Mood Disorders Laboratory, eventually becoming Professor of Psychiatry, Ophthalmology and Physiology/Pharmacology. In the Department of Psychiatry, he was appointed Vice-Chair in 1998 and then Senior Vice-Chair in 2003. In 2004, he became the Richard H. Phillips Professor of Biological Psychiatry. Upon his retirement in 2014, he became Professor Emeritus, Department of Psychiatry. He has published more than 240 scientific papers and book chapters, and he has given more than 410 scientific and professional

lectures, courses, and presentations. He has received several honours for his contributions, including a 2011 University of Chicago Alumni Professional Achievement Award for his work on the use of light and melatonin in the elucidation and treatment of circadian rhythm disorders, such as occur in Seasonal Affective Disorder and in totally blind people.

Professor Gerald Lincoln

PhD ScD FRSE (b. 1945) was brought up on a farm in Norfolk and followed his elder brothers Dennis and Roger into academic careers. His first success was the award in 1964 of the Prince Philip Prize for zoology from the Zoological Society of London. After reading Zoology at Imperial College London, he gained a PhD degree from the University of Cambridge in 1972, mentored by Professor Roger Short. The thesis was based on work on red deer on the Isle of Rum. This kindled a career in chronobiology. The research was then funded by the Medical Research Council at the MRC Centre for Reproductive Biology in Edinburgh (later Human Reproductive Sciences Unit). The aim was to unravel the mechanistic basis of seasonal breeding – Nature's Contraceptive. He received medals from the UK Endocrine and Neuroendocrine Societies and was elected a Fellow of the Royal Society of Edinburgh in 1993. He joined the University of Edinburgh in 2005, and is now retired as 'Emeritus Professor of Biological Timing', working in nature conservation (www.puddledub.org/). His publications include Lincoln (2001/2, 2014) and Lincoln *et al.* (2006).

Professor Rob Lucas

PhD (b. 1968) graduated from the University of York with a BSc in biological sciences in 1989. He subsequently worked in the pharmaceutical industry for three years before returning to graduate study in the laboratory of Andrew Loudon at the Institute of Zoology, University of London. In 1996 he completed his PhD thesis in the field of reproductive endocrinology. He then undertook post-doctoral research on circadian photobiology under the mentorship of Russell Foster at Imperial College London, and obtained his first independent academic position in 2000 when he was awarded a Governors Lectureship in the Faculty of Medicine at Imperial College. He moved to a Senior Lectureship at the University of Manchester in 2003, where he was appointed Professor of Neurobiology in 2006. He currently holds the GSK chair

in Neuroscience in the Faculty of Life Sciences, University of Manchester.

Professor Norman Rosenthal

MD (b. 1950) was born in Johannesburg, South Africa. He graduated as a medical doctor with high honours from the University of Witwatersrand in 1973. He immigrated to the United States, where he did his psychiatry residency and became Chief Resident. In 1979, he joined the National Institute of Mental Health in Bethesda, Maryland, where he became first a research fellow and later a tenured researcher. It was there in 1984 that he led the team that first named and described Seasonal Affective Disorder (SAD), and pioneered the use of light therapy for its treatment. The paper subsequently became a citation classic and has been cited well over 100 times. He has authored or co-authored hundreds of subsequent papers on SAD, light therapy, and related topics. Along with colleague Thomas Wehr, in 1991 he was awarded the Anna-Monika Prize for depression research for his work in this area. He is also a best-selling author, whose book *Winter Blues*, now in its fourth edition, has been described as 'a classic work' by the *New York Times*. He has also written seven other books for the general public. He is currently Clinical Professor of Psychiatry at Georgetown University. He maintains a private practice in Bethesda, Maryland and continues to research innovative treatments for depression and other psychiatric disorders.

Professor Tilli Tansey

OBE PhD PhD DSc HonFRCP FMedSci (b. 1953) graduated in zoology from the University of Sheffield in 1974, and obtained her PhD in *Octopus* neurochemistry in 1978. She worked as a neuroscientist in the Stazione Zoologica Naples, the Marine Laboratory in Plymouth, the MRC Brain Metabolism Unit, Edinburgh, and was a Multiple Sclerosis Society Research Fellow at St Thomas' Hospital, London (1983–1986). After a short sabbatical break at the Wellcome Institute for the History of Medicine (WIHM), she took a second PhD in medical history on the career of Sir Henry Dale, and became a member of the academic staff of the WIHM, later the Wellcome Trust Centre for the History of Medicine at UCL. She became Professor of the History of Modern Medical Sciences at UCL in 2007 and moved to Queen Mary, University of London (QMUL), with the same title, in 2010. With the late Sir Christopher Booth she created the History of Twentieth Century Medicine

Group in the early 1990s, now the History of Modern Biomedicine Research Group at QMUL.

Professor Chris Thompson

MD FRCP FRCPsych MRCGP FRSA (b. 1952) qualified in medicine at UCL in 1977. After posts at the Maudsley Hospital and the Institute of Psychiatry, he was appointed Senior Lecturer in Psychiatry at the Charing Cross Hospital Medical School (1984–1988), before becoming Professor of Psychiatry at the University of Southampton in 1988 and Head of the Medical School from 2001. He was appointed Chief Medical Officer of Priory Group in 2004 and Director of Public Affairs in 2012. He was one of the early SAD researchers, having SAD clinics, first at Charing Cross Hospital and then at the University of Southampton.

Dr Thomas Wehr

MD (b. 1941) received his MD from the University of Louisville School of Medicine in 1969. After a residency in psychiatry at Yale University School of Medicine he was based at the National Institute of Mental Health in Bethesda (NIMH) from 1973 until his retirement in 2003, where he was Chief of the Clinical Psychobiology Branch from 1982 to 1999 and then Chief of the Section on Biological Rhythms. He is currently Scientist Emeritus and in private psychiatry practice in Bethesda, MD. His research at the NIMH focused on the prevention and treatment of mood disorders, and his group was the first to describe SAD and demonstrate that the depression responds to light treatment. He was awarded the Anna-Monika Prize in 1981 (with Anna Wirz-Justice) and 1991 (with Norman Rosenthal) for research on depression.

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