History of Modern Biomedicine Research Group
School of History, Queen Mary University of London
Mile End Road, London E1 4NS
website: www.histmodbiomed.org

AUDIO INTERVIEW TRANSCRIPT

Arendt, Josephine: transcript of an audio interview (17-Mar-2015)

Interviewer: Tilli Tansey

Transcriber: Debra Gee

Editor: Tilli Tansey

Date of publication: 09-May-2017

Date and place of interview: 17-Mar-2015; Queen Mary University of London

Publisher: Queen Mary University of London

Collection: History of Modern Biomedicine Interviews (Digital Collection)

Reference: e2017153

Number of pages: 27

DOI: 10.17636/01022713

Acknowledgments: The project management of Mr Adam Wilkinson and the technical support of Mr Alan Yabsley are gratefully acknowledged. The History of Modern Biomedicine Research Group is funded by the Wellcome Trust, which is a registered charity (no. 210183). The current interview has been funded by the Wellcome Trust Strategic Award entitled "Makers of modern biomedicine: testimonies and legacy" (2012-2017; awarded to Professor Tilli Tansey).

Citation: Tansey E M (intvr); Tansey E M (ed) (2017) *Arendt, Josephine: transcript of an audio interview (17-Mar-2015).* History of Modern Biomedicine Interviews (Digital Collection), item e2017153. London: Queen Mary University of London.

Note: Audio interviews are conducted following standard oral history methodology, and have received ethical approval (reference QMREC 0642). Related material has been deposited in the Wellcome Library.

© The Trustee of the Wellcome Trust, London, 2017

Arendt, Josephine: transcript of an audio interview (17-Mar-2015)*

Biography: Professor Josephine Arendt (b. 1941) is Emeritus Professor of Endocrinology in the University of Surrey. Trained as a biochemist, she is a specialist on biological rhythms and has pioneered the field of chronobiology. She has researched biological rhythms and their mechanisms widely in animals and humans, including studies on jet lag, sleep disorders in the blind, shift work, and devised techniques to measure melatonin and its metabolites. In this interview and associated material, she describes her career and discusses many of these fascinating aspects of her work.

TT: Tilli Tansey

JA: Josephine Arendt

TT: For the record, 17th March 2015, interviewing Professor Jo Arendt in Queen Mary University of London. Thanks very much for coming, Jo. This has come about really because of our Witness Seminar which we held on SAD [Seasonal Affective Disorder], but of course that's just a tiny part of your larger research programme because you've worked in a tremendous array of areas. So could I ask you go back to the beginning and think about how did you first get interested in science and developing a professional career in science?

JA: Okay, well let's crawl back to 1962 when I emerged from university, with a degree in biochemistry and was looking for a PhD place. I graduated from University College London [UCL] and, for whatever reason, I've always been interested in neuroscience but I graduated in biochemistry. I ended up in the lab of Professor Merton Sandler at Queen Charlotte's Hospital in Goldhawk Road, working on tryptophan and its metabolism to 5-hydroxytryptamine (5-HT) or serotonin, and 5-HT wasn't then known to be a neurotransmitter in 1962. And in fact I managed to separate out the D- and L-isomers of commercially available tryptophan; it was my first ever publication and the only one I've ever had in *Nature*. So I was quite pleased with that. And because of course it's the L form of tryptophan - which is the precursor of serotonin - that was quite important from the point of view of metabolic studies. At the time a chap called Aaron Lerner discovered a new hormone (by processing, I think it was 350,000 pineal glands), which he called melatonin (chemically, *N*-acetyl-5-methoxytryptamine). And Julie Axelrod at National Institutes of Health [NIH] found that melatonin was derived from serotonin, which was my Thesis subject. And a very fascinating molecule it was because it causes frogs' skin to blanch. They have stellate melanophores in their skin, which are black, and when the star formation of the cell is expanded the skin is very dark, and when you drip a little melatonin on them, they scrunch up into little balls and the skin goes very pale. And it's exactly the opposite of what melanocyte-stimulating hormone does. So it was known to lighten frog melanophores, and that was its only known function at the time. In fact the pineal itself was considered to be a rudimentary vestige. Descartes of course said it was the seat of the soul, and that's coloured the field ever since, but it was a jolly good neuroradiological marker, because it calcifies usually in most people early in life, and that was about all it was useful for. However, the discovery of this hormone was really fascinating, and because it was derived from serotonin, I took my first opportunity to look for a grant to work on it.

---

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 17 March 2015, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey.

Now, in between times, we had moved from England to Switzerland to the University of Geneva; in my case I applied to the Paediatric Clinic in Geneva to see if I could do some neuroscience work related to melatonin in a brand new research facility. They said, 'Yes, very interesting, providing you can find a link with our interests. And our interests are paediatric endocrinology.' Pineal tumours were associated with precocious puberty, and at that time a lady called Virginia Fiske had shown that the pineal appeared to be influenced by light and light affected the ovaries and light might possibly influence this hormone melatonin and so to connect endocrinology with my indole expertise was this little loop: serotonin, melatonin, possible light effects, reproduction, puberty. And I applied for it and got a grant to develop a measurement system for melatonin. The only way of measuring it at that time was by dripping it onto frog/toad melanophores, and a very tedious procedure it was. I had a whole breeding system for *Xenopus laevis* (the African clawed toad) in the lab and initially used the tadpole melanophore reaction to melatonin as a bioassay. Each point on the calibration curve required looking at 30 tadpoles separately under the microscope. But it was very sensitive - to 10^{-12} pg/ml. It was quite hard to get the money.

TT: Where was the grant from and how did you get that?

JA: I applied to the Fonds National Suisse de la Recherche Scientifique and their first answer was 'No.' And I don't think anybody's alive now who actually gave this answer, but someone said, 'The reasons were that I was foreign, I was female, and I had a family.' Wouldn't be allowed these days, I don't think.

TT: The three F's.

JA: Yes. I protested and they sent me to see Professor Alfred Pletscher, who was Head of Research at Hoffmann La Roche, and then Head of the Fonds National Suisse (Swiss National Science Foundation), and was very much a neuroscientist. I must have convinced him that it was worth supporting me, because I got the grant and set off to measure this difficult hormone. The Department I attached myself to, which was Paediatric Endocrinology, were experts on radioimmunoassay; a measurement technique based on the reversible binding by antibodies of antigens - other molecules. Small molecules like melatonin are not in themselves antigenic. However, when a small molecule is attached to a large protein molecule, it becomes an antigen thereby which produces antibodies on injection into say a sheep or a donkey or whatever. And the antibodies can be very specific in recognising the small molecule and not necessarily the larger one. This was the standard technique at the time to measure steroids like oestrogen and testosterone, and in fact Berson and Yalow had got the Nobel Prize for developing this technique.

It's extremely sensitive and we knew we were going to have to measure down to 10^{-12} at the time, because we knew potentially how much melatonin was going to be in the body from frog measurements in the pineal. And so I went for the most sensitive technique and we were lucky. Conjugating a molecule like melatonin to a protein is not particularly easy, because it's highly lipophilic and you have to put a carboxyl group or an amino group on it or something. And it just so happened that in Geneva at that time there was a little lab called Plan who made *N*-acetyl-5-methoxytryptophan which is melatonin with a carboxyl group attached to it. And we were able to link through that with a peptide bond to a large antigenic protein, and we got antibodies to melatonin. And then radioimmunoassay works on the principle, in this case, of a radioactive label (that is we had to make melatonin itself radioactive), and the measurement is the displacement of the radioactive melatonin bound to the antibody by whatever melatonin is present in the tissue or fluid that you're measuring.

So we had to make a radioactive label and I managed - after being incredibly careful - to make the first tritiated melatonin with tritiated acetyl-CoA, which was highly radioactive, and I managed two Curies per millimole which is not very much. Not for radioimmunoassay. I'll never forget this moment actually when we had one of these old-fashioned radiation counters called a Tricarb, and it counted β-radiation and γ-radiation. There was a little switch which changed the counting from γ to β and *vice versa*. And after working away at this synthesis and getting a minute amount of what I thought might be the right thing, I put it into the counter, turned it on and there was nothing there. Ah! And then I suddenly realised I'd got it on γ-radiation, not β, and switched it over to beta and there it was. It was as radioactive as it was possible to be

at the time.

TT: Can I just ask you what time this was. Are we talking about the early 1970s?

JA: 1973. I got the grant in 1972.

TT: Could you say a little bit about that, because you had a little bit of a jump from Merton's lab, then to University of Geneva?

JA: We liked Switzerland, and we both got jobs in Geneva. My husband got a job at the Cyanamide European Research Institute and I just went for whatever was going, and initially there was a research job in biochemistry at the École de Chimie under one Professor Theodore Posternak, who was a lovely man, and it was to work on meso-inositol. And it was rather dull, and I was very happy to have a reason to get out of it. The best thing about working in that lab was that he had a villa on the lake of Geneva with its own jetty and beach, and he used to invite the lab.

TT: That sounds very pleasant.

JA: Yes, so it was great.

TT: But you then got the grant to work at the Paediatric Clinic on melatonin measurement and to develop the radioimmunoassay for melatonin. You were very much at the cutting edge. You were very much a pioneer?

JA: Pretty pioneering, yes. I think that's right. As Norman [Rosenthal] said, and this was long before Al [Lewy] produced his GCMS [gas chromatography-mass spectrometry], his was published I think in, let me think, was it 1978? Well, I started work in 1972 and it worked in 1973 and it was published in 1975 and there was a big conference in Jerusalem in 1977. Julie Axelrod was there and knew then about this radioimmunoassay; another one was then published from Australia in 1977, oh, and one in America. But they were all after ours. I mean we didn't really know if it was going to work or not. I remember Dick Wurtman telling me (and we're still in contact occasionally) 'You can't make a radioimmunoassay for a molecule the size of melatonin!' As Norm says, absolutely rightly in his text for this meeting, it was considered probably quite mad, but anyway, it worked.

TT: How influential was it at the time? Did lots of people then pick up on that, pick up on your techniques for developing other assays?

JA: It's a very niche area, the pineal gland.

TT: That's what I was thinking, yes.

JA: Not now. But not because of the pineal, but because of melatonin itself. There's a whole school and vast numbers of publications on melatonin, but the pineal is still pretty much a niche area although we do know what it does now, what it's most important function is. And you know, once we had a measurement system going it just opened all the doors. And some people were really interested in this, and they were people like Fred Turek who was interested in the endocrinology of melatonin; and people like Lennart Wetterberg, who is mentioned several times in the text [see Overy and Tansey (2014)], who was interested in SAD. And this is before Norm's publication. Wetterberg was interested in depression generally, he was Head of the St Joran's Hospital at the Karolinska Institute, which is a psychiatric hospital. He phoned me up the day after the paper was published, and said, well, you know, 'I would really, really like to measure melatonin. What can you do for me?' And he had lots of strings he could pull. And one in particular was a company called KABI, which was a Swedish company which makes reagents. And he immediately got them to synthesise an antigen on the lines that we had done it, although they may have used a different technique - I never found out exactly how they did it - and they also raised an antibody.

And it turned out it was somewhat better than my first one (but mine was still the first!). And so we worked with Lennart Wetterberg in collaboration, because he had access to clinical samples and we were in real difficulty with access because it was a paediatric clinic. And once this assay was up and running, because we knew that the light was involved, almost the first proper experiment I did with it, was to get all the lab to come to my home sit them in darkness up to midnight, and take blood samples before and at the end of darkness on one occasion, and then on another occasion, sit them in room light, up to midnight, and take blood samples before and at the end of light. We wished, to see if light affected human melatonin. And because it was room light, it wasn't strong enough. And it didn't, although if I reanalyse the data (I've still got it, this was in 1975), I could probably find a little decrease. And, in fact, room light does affect it a little bit with a very sensitive assay system. But this is of course before Al and his paradigm shift stuff. Lennart Wetterberg also used light up in Stockholm and he claims, or has claimed in public, to have shown that light suppresses melatonin in humans for the first time, but it was an "n" of one. And you know, some people will only accept data when you've got statistical significance.

TT: When you were in Geneva, in the mid-1970s you've got this confluence of different techniques. I mean it looks almost obvious now, doesn't it? But it probably wasn't at the time. So you're a trained biochemist, you've got an interested in neuroscience, you've already got the practical techniques, the measuring techniques and you're in an institute where there's endocrinology coming in, there's some clinical work going on, then now you're getting into light as well. So you're working on the pineal, which is this rather mysterious organ at the time. So there's a lot of things going on. As I say, one would look now and say, 'Well, this is all obvious.' It wasn't at the time.

JA: It wasn't particularly. But the light connection was definitely there because we knew from Wilbur Quay's work and also from Helena Illnerova that there was a strong rhythm in the pineal, of 5-HT (that's serotonin), that it went down during the night and up during the day. And from the work especially of David Klein and Helena Illnerova that *N*-acetyl-transferase the rate limiting enzyme in melatonin production had a high amplitude rhythm in the pineal - the opposite to that of 5-HT, and was suppressed by light.

TT: And this is all human measurement?

JA: No, this is rats. And we knew that serotonin was the precursor of melatonin and we expected melatonin to be made at night in people. In our first RIA [radioimmunoassay] paper (1975) we looked at night and day melatonin in people and it was higher at night. Some brave people at MIT [Massachusetts Institute of Technology] using the tadpole bioassay, Harry Lynch working with Dick Wurtman, did publish in the same year as our radioimmunoassay came in (1975), that there were higher levels of human urinary melatonin at night than in the daytime. So we knew there was a rhythm, and because it was night-related, we expected light to be important.

My remit at that time, because it was a Paediatric Endocrinology Unit, was to see if it had a role in puberty in order to fit in with the interests of the clinic. And we did this: quite a lot of careful work looking at pubertal samples, but they were never, at that time, done properly by frequent sampling throughout the night in very dim light. It's jolly hard to get clinicians to take samples in the middle of the night. And we, at that time, never found a difference. In fact, it does go down in children before puberty, and there was a link proposed that it was responsible for the timing of human puberty, but that's absolutely never been convincingly demonstrated. But it certainly does help to time puberty in animals. And this is where the light comes in again because at this point, two really important things happened: we knew from early pioneers and Gerald Lincoln's work for example - and Brian Follett in fact, although he was birds really - that duration of the day, day length, governed the timing of seasonal reproduction in what are called photoperiodic species, and this includes sheep, it includes hamsters, mink, horses - vast numbers of animals govern their reproduction by the day length.

And when we found nothing of any real interest in human puberty at that time, it was clearly important to work on something which clearly responded to light. And at that point we moved back to England. Now

there's other stuff in-between times. There was, in the mid-1970s, well actually 1972, Joe Herbert in England, in Cambridge, and Klaus Hoffman in Munich, at the Max Planck, were both involved in showing that the pineal was involved in the timing of seasonal reproduction in ferrets and hamsters. They didn't know for sure that it was melatonin, but did know it was the pineal. So we have day length, melatonin being made at night in the dark phase, this has got very little at the moment to do with SAD, are you sure it's alright?

TT: Well, as far as I'm concerned, this interview is not about SAD, it's about you.

JA: Okay. Gosh, alright. Very nice of you, golly. Where was I?

TT: So you were talking about the influence, so you're now summarising the other things that had happened…

JA: That were happening…

TT: With Herbert, with the day length…

JA: That had come together.

TT: The dark phase of melatonin…

JA: Being associated with night, therefore probably associated with photoperiod: photoperiod times reproduction. And in 1974, Dave Klein, still a very good friend, and Joan Weller, published with Robert Moore, a series of papers showing that the rhythm of the melatonin pineal production was governed by the suprachiasmatic nucleus, the central clock so-called, or pacemaker in rats. And a bit later (1977) we looked at pineal synthesis of melatonin - this is in rats - blood melatonin levels and pineal melatonin levels. In other words, we looked at the enzyme in the pineal, the hormone in the pineal and the hormone in the blood simultaneously in rats, through 24 hours, and that was a night to remember, I can tell you.

And they show a beautiful, beautiful correlation. So you have the synthesis is going up, the pineal melatonin going up, and the blood melatonin going up. So we knew that, whatever is going on in the pineal appears in the blood, and therefore because the suprachiasmatic nucleus - the clock - governs the pineal rhythm, that we have an external peripheral clock marker. And this was way back in the mid-1970s. So that was pretty exciting.

TT: So this was when you were still in Geneva, and then you returned to England?

JA: Yes, we did the rat experiment in Geneva. In fact, we got into a bit of trouble over it because my companion - I had a colleague called Mike Wilkinson, he was a post-doc then. He's a Prof. in Nova Scotia now. We smoked and we set off the smoke alarms in the building at three o'clock in the morning, and I don't know how many fire engines they sent.

TT: Can I ask you a general question that may have relevance to other parts of your career, animal experiments: what were the regulations in Geneva? Was it any different from this country?

JA: I never had to fill in a Home Office form in Switzerland or in France. Never as far as I know, but it is possible that the whole institute was licensed in some way, and I just was not aware of it.

TT: So let's go back to your career, Jo. So you've come back to the UK and this is what, late 1970s?

JA: We left in 1977. I wanted to come back, but in fact, my husband didn't. However, he found a job first. I should say at this point that my professional life would not have been possible without his acceptance and help, especially later when it came to looking after my very elderly mother.

TT: May I ask, is your husband an academic? Was he in the same field?

JA: He was a research chemist and he was at one time Head of Research at the Paint Research Association until he packed it all in and got thoroughly fed up with chemistry, and went off to be an administrator on the island of Guernsey, where I happen to come from. And he's been there ever since. I couldn't work there.

TT: So you were both working in Geneva and then you came back to the UK?

JA: After the Cyanamide European Research Institute he worked at the Battelle Research Institute. There were several of them (Battelle Research Institutes) at the time. It's American. Developing polymers and things like that. So yes, we came back because, or mostly because, I suppose, one comes back for children's education and elderly parents.

I looked for somewhere that would suit me. He looked for somewhere which would suit him, and it so happened that the Paint Research Institute was in Teddington and the University of Surrey had a big radioimmunoassay group under Prof. Vincent Marks, who you have probably come across?

TT: Yes.

JA: I asked the Swiss if I could take technicians and money and my spectrofluorometer back to England with me, they let me take the technician and quite a bit of the grant. And so I was welcomed with open arms (I think!).

TT: What about the equipment?

JA: I wasn't allowed the spectrometer. I did try. But in fact it wasn't necessary at the time, by then we were using the RIA full-time and developing new ones. Vincent was keen on getting this; I think he phoned up one of his friends at Bart's, John Landon, who said, 'Ah, melatonin, it's the hottest thing since, sliced bread. Melatonin plus money?'

TT: What is there not to like? [Laughter].

JA: I never had anybody come to my group with, you know, project and money. So, there you are, I was given lab space and so on and so forth. But it so happened that at that time, Vincent was very entrepreneurial - still is, in fact, in his eighties. He'd set up to use an Occupational Therapy Unit to make antibodies and it was at Hurstwood Park Mental Hospital. And because it was National Health Service [NHS] Hospital, all the animals were looked after by the patients (no doubt with help). But the reagents that came out of it, the reagents that came out of it were supplied to the NHS.

TT: I've never heard of any such thing.

JA: Well, we had good times down at Hurstwood Park, because we ate the odd sheep, you know when we had a summer barbecue. It doesn't exist anymore. It was a 16th century (I think) beautiful old farmhouse with a huge amount of land, and I think the NHS thought it would like the money. Anyway, there you go. Please note that this is all from memory, and I hope that there are not too many errors and inaccuracies.

TT: And this was already set up when you arrived there?

JA: Yes. Vincent had set that up and before I could get myself back to Surrey he said, 'Send the antigen over.' So I sent it over and his Chief Biochemist, Brian Morris, who did the business with the sheep, immunised quite a few sheep and when I arrived back in Surrey, we had a new antibody on the way - two in fact - which we are still using. Yes, Hurstwood Park was fun. So I then acquired a whole batch of new antibody; this is now the third anti-melatonin antibody we used. One was the original one in Geneva; then there was the one in Stockholm, KABI, of which I had a free supply; and finally, the Guildford antibody.

Vincent had, at this time, set up a company to sell off any antibodies surplus to NHS requirements. So I set up my own company.

TT: Yes, I found your website, yes. This is Stockgrand?

JA: Stockgrand. It's an off the shelf, £250 company, all set up in 24 hours. This was in 1988 and it has been enormously important, because it provides bridging funds. It has in fact supported wholly some PhD-students and partly many more - 18 I believe - it enables us to go to conferences and things like that.

TT: Those things, those little bits of money, just having that little bit of a safety net is incredibly important.

JA: And also, this does relate to SAD now a bit, because when I moved to England somebody told the Maudsley there was a melatonin assay in England. There weren't many around at that time. There was one in America, one in Australia, one in England and one in Canada. And Stuart Checkley got in touch. I think I've already mentioned I knew Anna Wirz very well at that time. She was in Switzerland at the Basel Psychiatric Clinic, and she'd gone to work at NIH with Tom Wehr and Norm Rosenthal. And so, I had a direct personal connection, because I'd met them all at conferences.

Stuart wanted to, just to collaborate and so we did quite a bit and we had a joint PhD-student, Chris Franey. Chris did a great job developing the RIA a bit better. And then we looked at Stuart's patients, under different treatment regimes with light, and under different anti-depressants. Chris Thompson was at the Maudsley at that time and then, I think, moved out to Southampton and we continued to work with him because he was interested in the light sensitivity, as measured by melatonin suppression, of his SAD patients. And Stockgrand, in addition to selling the reagents, offered an assay service. After a bit I thought, 'Well, this is not actually doing my academic career a lot of good. It's interesting, but it's not my work, it's their work,' which is why I was very honoured to be invited to this meeting, I really was. Mine was the Antarctic side of it and the sheep side, and then, the melatonin chronobiotics side, but I'll have to backtrack on that, won't I?

TT: Yes, we want to go into that.

JA: And so I thought, 'Well, why don't we just do assays for money, and I'll employ somebody to do it,' which we've done ever since. In fact, I've just set up another company, because I'm not often in Guildford these days, Stockgrand now holds the reagents only, it doesn't do any assays. But there's a new company I've set up called Surrey Assays, which is run by the major shareholder a lovely lady called Benita Middleton, Dr Benita Middleton, who has been my right hand lady for years and years and years, with myself and also the person who took over my research group, Debra Skene, Professor Debra Skene also as Directors. I really can't take the major responsibility when I'm not there. It's all very well keeping stuff in the deep freeze, but assays you have to have all sorts of assurances and professional indemnity.

TT: Can I just ask you, what kind of position did you have? Did you have a formal academic appointment at this point?

JA: Initially, I had a grant to pay my salary from the MRC [Medical Research Council], I think.

TT: But did you apply for your own salary, can you remember? Or was it something Vincent Marks did for you?

JA: He didn't have a job for me at the time. No, the Swiss I think paid me for a bit while I got going, and then I put in a grant to do further RIA development of the major melatonin metabolite, and another one called 5-methoxytryptophol, which are all related to melatonin. And the melatonin metabolite was really successful, that was a terrific project and it's gone all over that world, that assay. Other people have, of course,

developed them since, but we did it first. I have to blow my own trumpet otherwise you just get lost in the literature. Students don't cite anything that's older than ten years these days. That grant enabled me to take on Debra Skene, then a post-doc, to develop the 5-methoxytryptophol assay. She took over most of my group when I officially retired, and we worked together from 1984 with an interlude when she worked for Prof. Paul Pevet in Strasbourg.

TT: Even ten years is quite a long time nowadays.

JA: That's right. And if somebody writes a review, they cite their own review; they don't bother to refer to the original literature. And I think, 'God, look at all that work we did.'

TT: Well, that is one of the reasons we do these interviews and the Witness Seminars, to actually try and record the work that people do.

JA: It's great, and it's digitised, it's modern, it's accessible. It's terrific!

TT: So you then had an MRC grant that was paying your salary?

JA: Yes. I think it paid my salary, but it certainly paid for the project. But at some point, Vincent found a job called "Experimental Officer". I'm talking now about 1980, yes, 1979, 1980, so I must have had a couple of years of project grant. The Wellcome Trust stepped in at one point, because I had a Wellcome grant: they paid my salary for several years on condition that the University took it over when the Wellcome money came to an end.

The Wellcome Trustee Stan Peart - I have a lovely letter from him which I have kept and which I have looked up. This was 1986ish when I published the first treatment of jet lag with melatonin study. Nobody believed it. Now half the world uses it. And I applied to the Wellcome for a project grant, to see what melatonin might potentially do to circadian rhythm this, circadian rhythm that for the therapeutic possibilities. And I didn't get it, but he wrote me a really nice letter saying something, 'You'll get it one of these days,' or words to that effect. In other words, I think he was favourable, but the prevailing opinion was that melatonin was a waste of time. I also applied to the MRC for a programme grant which went quite a way down the line, but in the end was not successful. People used to say things like, 'Circadian rhythms? That old chestnut.' It's funny, isn't it how things change?

TT: Could you say a little bit more that you just mentioned there en passant almost, the jet lag study?

JA: Well, let me tell you how I got into it. Yes, so in 1980, much stressed out, I developed breast cancer. I had a full mastectomy and felt dreadful afterwards - I couldn't sleep. And we knew that melatonin had possibly some anti-cancer effects and I knew then that it would shift rhythms in sheep, I haven't talked much about the sheep but they were very important. And so I thought, 'I'd better take some melatonin.' And I did. And it worked, n=1, but there's lots more evidence these days. It made me sleep when I wanted to go to sleep, which it does for delayed phase sleep syndrome in people now. Whether it did anything for the cancer, I don't know, but I went 28 years without any recurrence. I had uterine cancer five years ago, which the original breast cancer is a risk factor for, but I'm still here. So having taken it myself I persuaded my good friend, a clinician called John Wright to take it as well and he also said, 'Interesting.' And then, without any money really, I said, 'Well, I'm going to do a proper clinical trial of this stuff, because if it shifts rhythms it has potential therapeutic value.' And I'm talking now 1982. And I recruited 12 of my colleagues at Surrey, with ethical; no I'm not sure I did have ethical permission for it.

TT: Probably not in those days.

JA: No, probably not. To take it (2 mg) every evening in early evening, and we didn't know how long we'd have to take it for before it had an effect but we knew that, and I haven't talked about the sheep, but it took at least a month to have an effect on sheep's reproductive rhythm timing. So we thought we'd better give it

them for a month every evening [laughs]. I was very lucky to get all these volunteers; I don't think they'd do it these days.

TT: I don't think so. And you probably wouldn't get Ethical Committee approval.

JA: No. A drug? What's it do? Shrinks hamsters gonads? [Laughter]. In fact someone wrote an anonymous review in *The Lancet* about melatonin saying it shrank hamsters gonads and was probably not a good idea for people. So the first proper study we did was to see if it really works on more than one person, two in fact. Does it have any nasty side effects? How long, well we didn't know how long we'd have to take it for, but they took it for a month and it was a double blind, randomised placebo controlled trial. I didn't have an intention to treat in there, but it was as careful as we could do it. And it made people feel sleepy earlier in the evening, but most importantly, when we could distinguish the endogenous melatonin rhythm, from the exogenous, it shifted the endogenous rhythm; it advanced it. You couldn't see it in everybody because of variable metabolic clearance rates, but you could see it in five of our 12 volunteers: a clear advanced circadian rhythm shift. And at this point, it was Vincent's idea, I have to admit, I applied to do a CIBA Foundation Symposium on the subject of photoperiodism, melatonin and the pineal, in which it was first published. The Symposium was in 1984, it was published in 1985 - CIBA Foundation 117 - in which there's all sorts of really interesting stuff on sheep and the first chronobiotic effects of melatonin on shifting rhythms. And then, having personally been convinced that melatonin could shift rhythms the next thing was, wouldn't it be fun to do a jet lag study?

There's a chap called Stuart Armstrong in Australia who, whilst we were doing our melatonin chronobiotic stuff in 1982, was doing rat melatonin chronobiotic stuff with his PhD-student Jenny Redman and the first rat data with Jenny Redman as first author came out in 1983, whereby you could synchronise a rat's free running sleep-wake cycle with melatonin. But also in 1983 the idea that it would do that in humans had been published by us in *BMJ* [*British Medical Journal*] and I had also written this for a rather obscure publication which Merton Sandler asked me to write for, and indeed we were doing the preliminary work for it. But Stuart got his paper into *Science*, synchronisation of rat circadian sleep-wake cycle. So it was all in the air. I think these things happen like that, don't you?

TT: Yes, yes.

JA: They sort of arise all over the world.

TT: Yes, and lots of different people. And it's curious as to how and why. One of the things we are trying to explore is what did happen and why do these things take off at a particular time? Because ten years earlier, it wouldn't have happened.

JA: No.

TT: And ten years later been overtaken by other things.

JA: And again, Vincent was helpful there. He had a contact, now where was it? On the *Financial Times* [*FT*] I think, and they put a little thing, I think it was in the *FT*, 'The University of Surrey wants to do a jet lag study and is looking for sponsorship.' Or words to that effect. And through that, I got free flights from British Caledonian airways, some free hotels, including the Mark Hopkins Intercontinental, which is one of the poshest ones in San Francisco, several other small sponsors especially Horner Ltd Montreal (Dennis Jones), and no shortage of volunteers. And we had enough money to send, how many was it, 17 people to San Francisco, and made them stay there a fortnight to adapt to West Coast time. Now this ensured we got volunteers, of course, and we did the study on the return journey, so we could do all the measures in Guildford. They didn't all go at once, but they went in groups and they were nearly all my colleagues at the University of Surrey. But I did also send my mum, and I sent my husband, and I was told I shouldn't have done that. What the hell, you know? It was fun! It was really good fun doing this. And Alex Borbely in Zurich lent me I think the very first actigraphs, these are small wrist monitors which measure activity and

rest moments and tell people how they sleep. And you know all this personal health monitoring these days? They were sort of at the beginning of all of that, and they're extensively used by sleeps labs now to see how interrupted people's sleep is, because when the actigraph doesn't measure anything, either you're watching a film or you're asleep, or your arm's paralysed, or whatever, if it's not moving for long enough.

So we had the actigraphs to get an objective measure of sleep and we had to then send them to Zurich as soon as they got back from San Francisco, because Alex had the only way of downloading them and seeing how the sleep was. We got them to collect their urine every four hours during the day and overnight, so they walked around the west coast of California carrying bags of pee. They didn't seem to mind too much. And they did that for several days before they left so we had a baseline to see if they were entrained to California time, and then, of course, sequentially for one week, and then 48 hours a week later, and 48 hours a week after that, when they got home. Why did we collect urine? Because by then we'd developed this new assay for the melatonin metabolite (PhD-student Chris Bojkowski) which reflects melatonin beautifully as well. It's pretty good in hourly urine samples, but most people can't be persuaded to give you hourly ones. But it's really quite good if you just collect sequential urine throughout, usually 48 hours, but in some cases on the North Sea oilrigs we've done it continuously for two weeks. Can you imagine? I had two PhD-students on this project, the last one got, all told, 65 men to collect sequential urine samples [laughter]. For two weeks continuously.

TT: Was this a male or female student?

JA: The last one was female. That helped.

TT: Yes, I think it would [laughter].

JA: I have personally collected 48 hours' sequential urines from a ship's crew at weekly intervals for six weeks in the South Atlantic - they were wonderful volunteers. Anyway, going back, we had urine to measure melatonin metabolite to decide if the treatment with melatonin or placebo retimed your clock to UK time coming back from San Francisco to London. Did it speed it up? And it did. Just significantly. A huge variability, though. And we published this in the *BMJ* at which point all hell was let loose. I mean the media just went absolutely bananas, and I was a sort of bad smell as far as the field were concerned. What a lot of rubbish, you know, taking your friends to San Francisco. Give you melatonin. Complete crap. No proper controls *etc.* [laughter]. However, there has been a meta-analysis - several in fact - but the best one's the Cochrane database, which says it works and there have been a lot of studies since then. You've got to get the timing right and you've got to know approximately what circadian phase people are in in order to get the timing right. And then it really does work. But knowing the approximate circadian phase is the problem. And what we really need - and this is one of the things I've really pushed for and we haven't got there - is a biosensor to spot-test circadian phase. And some Canadians are working on this at the moment with one of our antibodies, but they haven't got the sensitivity yet.

TT: Well, I do want to talk about the comparative aspects and the sheep, because you've mentioned Gerald Lincoln and also Brian Follett, but of course that was mainly birds. There is a whole other area of people working on photoperiodism and circadian rhythms, which are all the zoologists and the animal behaviour people.

JA: Well, this is the real function of the pineal gland and we're going to scroll back now, having done quite a bit of human chat. When I arrived in Surrey I discovered that there was a sheep reproduction expert there called Andy Symons, and he was only too happy to set up a joint grant because we knew that sheep bred according to the length of the day. So the idea was let's look at melatonin in sheep to see if it changes with the length of the day, and we didn't know that in 1977. And then take it from there. So I had an AFRC [Agricultural and Food Research Council] grant with Andy and we did at least ten years' worth of sheep reproduction in which you could show very clearly the change in duration of melatonin throughout 24 hours in the course of the seasons - longer profile in winter - and then the next idea was, well, if we give them a winter melatonin profile in the summer (sheep breed in the winter), will they come into season? And they

did. We fed them melatonin in June in such a way (if you did the pharmacokinetics, which we did), that you could mimic the winter profile. So you have this little short peak of melatonin in June and you add to it, by feeding them some in the late afternoon, and they all came into season approximately six weeks later (much earlier than usual in the breed we used - Suffolk Cross). And, in fact, it's possible to manipulate the breeding season completely, but you also have to use light (photoperiod). And I don't want to go into this phenomenon called "refractoriness" - it's a bit too complicated. But it might be related to SAD actually, because Gerald had some very interesting comments to make at the end of that text. In other words, if you keep sheep in summer day length for long enough, even if they never see a winter day, they will come into season anyway because they've become refractory to summer day length. And, likewise, if you keep them in winter day length or if you like, winter melatonin, long enough, they'll become refractory to that and go out of season.

TT: So it overrides it.

JA: Yes. But by giving them early summer light in the spring and early winter darkness with melatonin or artificial darkness, you can reverse the breeding season completely. And this was, of course, of academic interest, but it's also a very commercial interest because you get better prices for early lamb than you do for late lamb. I didn't know about all this commercial aspect before we started, but I do now. And the other really interesting thing we never managed to get the money for was race horses, because every race horse's birthday is 1st January and, you know, if a two-year-old is born on 1st January, he or she is going to have an advantage over a two-year-old who was born three months later in March. Much more developed and more mature. So the aim of racehorse breeding, I understand, is to get mares to foal not before, but just after the 1st January and, theoretically, you can do that with melatonin and light and maybe somebody's done it by now; I haven't really followed the literature on that. But you can certainly reverse the breeding season, and I believe it is applied in France, and I think in Australia. Seamark and Kennaway did this in Australia, and I should say that the technique we used to give our animals melatonin, we picked up from Seamark. It was dissolved on little pellets, and just fed it to them.

TT: But you couldn't control the dosage presumably by doing that?

JA: Well you can, because they like the pellets and they will eat them very happily; only one pellet. And the rumen acts as a slow-release preparation - that was very convenient.

TT: Yes. It was almost, it's very convenient in a way that you went to Surrey, because there's this radioimmunoassay lab, and then the people working, and there's this one person who is an expert in sheep reproduction. Was it your idea to do the sheep project?

JA: Oh yes. Hardly anyone had heard of melatonin and what it might do in 1977. There wasn't a lot of biological research going on at Surrey at the time. It's enormously increased since then, it's one of the best, you know, it's not a Russell Group, but it's pretty good now, Surrey. So Andy and I, together, wrote a grant application to look at melatonin in sheep and we were generously funded by the AFRC for several years. I had the assay and the melatonin know-how, he knew about sheep and it was a really good collaboration, but he did probably too much teaching, he did a lot of teaching, a lot of admin, and he didn't really pursue it in the way that he could have done.

But at this time I was contacted by Prof. Isabel Forsyth who was working at the AFRC Institute in Shinfield, Reading. She was interested in the neuroendocrine control of reproductive function in goats, and with AFRC funding we investigated the roles of photoperiod, temperature and melatonin in reproduction and coat growth in dairy goats during the 1990s with our PhD-students Sharon Deveson and Fiona Gebbie. A goat's response is similar to that of sheep - photoperiod was modulated by temperature. But probably the most interesting observation was that we could demonstrate that pre-natal photoperiod dictates the timing of puberty postnatally. Thus, maternal perception of photoperiod was transmitted to the foetus.

Then the AFRC ceased to fund large animal physiology, at least the sort of stuff that we were doing. They

were more interested in embryonic stuff and molecular biology, and it's all gone that way anyway.

TT: Well, it wasn't just AFRC, it was everywhere. And it's a constant problem for whole animal physiologists, I think. It's beginning to reverse now, I think.

JA: There's not much point in the molecular biology without the…, what's the word?

TT: Without the context. So your career now, you've got the technical, the chemical, the assays…

JA: The sheep.

TT: Yes, so there's comparative stuff, and then there's the human stuff. There's a wide array. I mean this would nowadays be considered dangerously unfocused [laughs].

JA: Absolutely.

TT: You wouldn't be able to develop a career like this nowadays.

JA: I'm so sorry.

TT: This is part of the history, isn't it?

JA: It was all interesting. The main thrust was the physiological role and therapeutic potential of melatonin. But it was a bit opportunistic as well. I mean, having assays will do all sorts of things.

TT: Well, of course, Pasteur said, 'Fortune favours the prepared mind.' And you actually could see the links and be able to develop these.

JA: Well, it was a very good position to be in. It was hard to find funding, but the whole field was wide open and there was the SAD business going on, there were rhythms going on all over the place, there was the connection to NIH, the connection to the Maudsley. Yes, it was a busy time. But what was difficult, but it no longer is, was to do our own proper human experiments. And that first one I did on melatonin as a chronobiotic had to be done in people off site. You know, they went home with their melatonin or placebo and then they would come in for a 24-hour session of blood sampling and so on and so forth. We didn't have any proper human clinical research facilities except when on two occasions we could use a hospital ward. In fact, at one point I bought in six Z-beds, and put them in a very small room in order to give people light treatment in the middle of the night. That was our clinical research facility. And people, lots of people of our generation - my generation anyway - will tell you that their facilities were much like that, you know. 'Well, we had to do all our bird work in local coal cellar,' or words to that effect.

But people were very interested to collaborate on the clinical front at the time, and particularly the NIH connection, because Tom Wehr who didn't come to the SAD meeting, but is a really wonderful guy; he (and Norm refers to this), did this experiment whereby he kept people, not sheep, in 14 hours of darkness a day, solid darkness, for two months, and then two months of ten hours solid darkness. And he showed that people do what sheep do with melatonin: they have longer profiles in shorter days. That was all done through our company, the assays were done by Stockgrand.

TT: So can we talk a little bit about this NIH connection, because this is through Anna Wirz?

JA: Originally through Anna, yes.

TT: And through Anna, but you actually mentioned earlier that you'd already met Norm and Al at conferences. What kind of conferences? How did you start talking to each other, and how did you get into SAD?

JA: Okay. In 1977 Anna and I gave two related presentations, at one of the first ever chronobiology conferences in Pavia in Italy, which was run under the auspices of a chap called Franz Halberg. I won't go into it, one could spend a lot of time on Franz Halberg, but I won't. And at that conference was a chap called Dan Kripke, who is mentioned in your text, and Tom Wehr; both are psychiatrists interested in rhythms. Anna got on very well with Tom and she went to work with him. She was at the Psychiatric Clinic in Basel at the time, and she was actually at UCL. She did her PhD in plant phenols with Derek Banthorpe at UCL, about the same time as I was there, so there you go. And she and I have always got on ever since we met in Switzerland. So she went to work with Tom and took the idea of measuring melatonin over there, although at this point Al Lewy went off with Sandy Markey to develop the mass spectrometry assay for melatonin at NIH. I had met Tom as well at this conference. And then when both of them wanted to measure melatonin, they came to me. It was at one time, you know, the only assay available. And so we did quite a lot with them.

Anna had this lovely idea of how, maybe, in Swiss mountain valleys, depending at what height you live, you get a longer or shorter photoperiod in the winter. So she was looking at how going out for a walk in the morning in bright sunshine is light treatment. And she did lots of things like that. She was, and is, a very interesting lady. She and Tom got the Santa Monica Prize, in fact, for looking at depression in a new way. They had sleep-deprived a depressive - one person - and completely remitted their depression more or less instantly. And Tom had always been interested in the strange rhythms of bipolar patients and depressives, and this sleep-deprivation convinced him even more that rhythms were important to the manifestation of psychiatric disorder, but more specifically, affective disorder. And he seemed at the time much more interested in bipolar patients than other things. So rhythms were very strongly connected to psychiatry, and this is all simultaneous with us working on sheep in Surrey, and I took the sheep duration and breeding season change to a Gordon [Research] Conference at Colby Sawyer College in New Hampshire and, having already met Tom, I there also met Al and Norm.

And at that point British Antarctic Survey had already asked me if I would like to give the Base medic a research project in Antarctica, because he hadn't got anything to do. So I knew before the publication, because Anna was at NIH, I knew about the SAD story. So Al and Norm and I sat down on the beach, as you've seen from the photograph, and I said, 'Look, I've got this wonderful opportunity to do a project in Antarctica. It doesn't get much darker than that. I assume that they get depressed in the winter and I'm going to give them some light treatment. And what do you recommend? How long should I give it for?' They said, 'We don't know. We don't know, try giving it for six weeks' (as we knew this would change the seasonal status of sheep). So I did. And you can't get fit, healthy, young men to sit down for three hours in front of a bright light in the morning and the evening, as they did in treating the first SAD patients. I just did an hour morning and evening: a skeleton photoperiod. How much? Well, we used the amount that Al said completely suppressed melatonin. And at that time it was of such interest that a chap called Luke Thorington, who was Director of a light manufacturing company, Full Spectrum Lighting, donated the lights to take to Antarctica and paid for them to get there.

So we really did very well out of that one. We got the best possible advice, we got the lights, and at that time we were allowed to take blood samples in Antarctica, and so that's what I did. The base doctor, a chap called James Broadway, still in contact, good friend, Consultant Anaesthetist, he was brilliant, and we got three months to train him before he went, in what he was going to do. Give an hour of light, bright light in the morning, they've got to sit in front of it, they've got to be approximately a metre away from it, for 2,000 lux. (Rob [Lucas] will say, 'Oh, it's got to be in irradiance, you can't talk about lux,' but many clinicians still talk about lux. I appreciate his point, it depends on the wavelength). James did an absolutely great job. He took 24 hours' worth of blood samples in the winter in one group of people, in two groups of people in fact. There were enough to do two groups one being a dim light control. And so he had a baseline profile; nobody really knew what the lights were going to do at this point. And then they had to do it every morning, every evening, for six weeks, an hour of light in the morning and in the evening. And then he did another 24-hour profile blood sampling of each group. And during all of that time he did performance tests, he did alertness variables and VAS [visual analogue scale] scales. We didn't do sleep, which is a pity; we've done a lot since, but we didn't do sleep then. Simon Folkard was on board for the psychology. I don't know if

you've come across Simon? He was then working at the MRC [Medical Research Council] Psychology Unit at Sussex under Peter Colquhoun, and he told me he was the only chronopsychologist in the world - now there are lots. He's a great bloke as well - he taught me a lot about circadian rhythms.

And so off James went. We had the right to communicate once a month by Telex. Now they have got satellite phone calls on tap. And after he came back, the British Antarctic Survey paid for him to work in the lab to do the measurements, and work it up, and publish. And he did. And it was published initially as a reviewed abstract in *J. Physiol.* [*The Journal of Physiology*], it was a Phys Soc [The Physiological Society] presentation, introduced by Anne Warner in 1986. And the received wisdom at that time in the field was that light was not really important as a circadian rhythm time cue. And what we showed was a very clear circadian rhythm shift with light treatment. And in fact it was probably even bigger than it looked like, because they shifted the clocks on the base by, I think, three hours, but it's hard to find out in retrospect, and I think it would have been, as I say, an even bigger shift if we'd known about the clocks change. But, anyway, it was a very nice shift and published in the same year as that of Chuck Czeisler at Harvard who did a definitive study on light shifting circadian rhythms on a large number of people, but he does agree that we did this at the same time.

TT: I'm fascinated, Anne Warner was a good friend of mine. Why did Anne introduce it?

JA: Why? Because she's a friend of mine. She said, 'Oh, you've got to put that in the Phys Soc.' I think it was so. It's the only reason I would have had anything to do with the Physiological Society, as I was not a Member.

TT: No, it just seems odd, I mean before you become a Member, it's somebody in your own field who would introduce it. No, it's perfectly acceptable.

JA: I wasn't a Member, although I have become one since, because somebody called Abe Guz said, 'Why aren't you a Member of the Physiological Society?'

TT: He was a lovely man. He died last year. Yes, just before Merton in fact, I think. But you said that somebody had suggested, somebody from the British Antarctic Survey suggested you provide a project for the base doctor. How did that come about?

JA: My memory may not be entirely accurate. You may have come across one professor Roger Short. Roger was very prominent in sheep endocrinology at that time and he knew about our melatonin work in sheep. I really owe Roger one for this, I think the British Antarctic Survey asked Roger if he had any ideas for what somebody could do in Antarctica and I think he said, 'Why don't you ask Jo Arendt?' Because of light, dark, and melatonin and that's how it came about, I think.

TT: Can I ask you now to talk a little bit more about SAD? Because now, you've met, you've got Anna and Tom, you know them very well, you've met Al and Norm. So where does this, how does this take off, and what are you views about some of the things that were going on generally?

JA: Well, I had a problem particularly with the phase delay theory about at that time, which I think was published in 1987. Because at that time we'd done our first Antarctic work, and what you see is a major phase delay in the Antarctic winter. But they don't get SAD on the whole. So if you look at it from that point of view, lots of people get phase delayed in winter, particularly in our climate, as Jennifer Eastman was saying. You know we don't have snow, we have these miserable, dark days. And not everybody gets SAD. So one is not a condition for the other to develop. So there has to be something more than that to my mind. Phase delay, and, of course, as Al says, phase advance in some cases plus what? Some kind of vulnerability? Al has published in, I think, the *Annals of the New York Academy of Sciences* that there's a kind of sweet spot whereby people's circadian phase and their sleep has to be just right for them not to get SAD. So it's quite complicated. It's quite possible; I mean I'm sure if you orientate your circadian phase according to the time, it should best be timed for your sleep to be good, fine. But we find people who are often three, four hours

delayed from "normal" phase, when we're just screening normal volunteers, things like that. And I think other people will say the same.

So the fact is also that in Iceland, SAD is, well it's there but not very much. You'd expect them to get loads of it, wouldn't you? And there is a publication by Icelandic people that Icelanders who move to Canada don't get much SAD either. And there's, of course, a lot of interest in the genetic side of it. But I also think that like a lot of these things including delayed sleep phase syndrome, there's a huge behavioural component. But I'm not a psychologist, so I perhaps shouldn't say any more about that.

TT: Although this is the reason why we first met, SAD is only just one component of your career and the way it fits in. So if you want to conjecture about it or from your experience, by all means feel free to do so. I don't mind, Jo.

JA: Well, I mean I think there's a lot of it about. Our tendency these days, in particular, and I'm not sure how this will fit in with SAD, but you'll have heard about teenagers not being able to get up in the morning and how they're going to start school later? That wasn't true when I was a teenager, was it? I think that's behavioural. I think that's a self-induced delay by evening behaviour. Blue light in the evenings on the computer screen, no morning light, dopey in the mornings, *etc.* I'm sure many SAD patients have got a terrible problem, if it's not properly treated with light, and that their circadian systems might really not be completely balanced. But the behavioural correction is getting up for and exposure to the morning light, of course preferably morning light which is immediately alerting. And you don't shift phase immediately. There are things called "transients", so that there are both immediate and delayed effects of light.

TT: That's interesting.

JA: So I think there's a lot more to it than phase shifting, there's a lot more to it than being delayed in the first place, and the fact they put quite good films on telly late at night and a lot of people work shifts and have their circadian rhythms disrupted frequently. A lot of people fly around different time zones. We probably do real damage to our inside timing mechanisms and what that has in the way of psychiatric effects, well, who knows? But it is something that has been known for a very, very long time in the culture of particularly northern countries before the 24 hour society. Although it's not common in Iceland at all, it is common in Sweden. So it seems to me there's genetics, there's behaviour, possibly compounded by this sort of hyperphagia that they do tend to have, overeating, put on too much weight, look at yourself in the mirror and think, 'Oops.' Hard to get up in the morning, not much exercise. If you don't have to get up over the weekend, you can easily lose three or four hours, you know, and be very delayed on Monday morning. There's huge amounts of things all combined, I'm sure.

TT: Yes. So coming back to your involvement, so by the late 1980s, you've got fingers in lots of different research fields, haven't you? But do you see, I mean they're all together, there's common themes there.

JA: Well, it's all basically the circadian system.

TT: And is it chronobiology?

JA: Chronobiology refers to biological rhythms of any periodicity. Photoperiodism is based on the circadian system as well because it has to generate the 24 hour photo period changes inside you, as well as the 24 hour clock system. I mean I don't think humans are really different from other animals. They've presumably got some residual photoperiodism. I wrote an article about human residual photoperiodism in fact on, oh I don't know, a while ago now. And we tried to mimic long nights in humans with melatonin.

TT: Yes, I picked up a really good review in *Journal of Endocrinology*. I think it was from about ten years ago, yes. Very useful, Jo. I think it would be harder to explain if humans were very different from animals; much harder to explain.

JA: Yes, but Al doesn't accept this, and one of the things that I am convinced of - remember it's really esoteric, I'm afraid, perhaps from your point of view, but it concerns these two oscillators - the so called "dawn and dusk oscillators" (E&M) in animals, they're all over the place. In fruit flies even. Helena Illnerova, brilliant lady and a good friend, so you know I'm biased, but she has shown a clear two oscillator structure of the circadian system generating the melatonin rhythm in rats. And that you can modify it so there's a rise of melatonin, and there's the middle bit, and then there's the fall, and theoretically the rise is controlled by the evening oscillator and the fall by the morning oscillator. And you can adjust them differently from each other so that, for instance, if you give bright light in the early morning it cuts off the melatonin secretion and produces a phase advance of the morning oscillator which is bigger than the phase advance of the evening one, and the same applies in the opposite sense. So you can affect them differently. Both effects temporarily shorten the duration of the melatonin profile. And when I went on about duration of melatonin in humans probably being important, we don't really know too much about it with respect to SAD, because everybody uses the dim light melatonin onset now which is the circadian marker that Al proposed, and it's been very important, no doubt about that. He says he doesn't believe duration of melatonin has got anything to do with it, and that there's no evidence for two oscillators in humans, but there is in fact. And it may be the coupling strength of these two oscillators which is one of the features of this illness that we really don't know anything about, because it hasn't been properly studied, I think. But this is just me holding forth, I'm afraid.

TT: That's fine.

JA: I have got very nice pictures of human beings with double peaks in melatonin, strongly suggesting two oscillators. Most of them in fact come from Antarctica in semi-natural field conditions with hourly blood sampling for 24 hours. And our sheep clearly had two peaks in the winter, when the night's long enough. In the summer the profile coalesces into one peak.

TT: Yes, fascinating. So if we come back to say the late 1980s, early 1990s, there's, are all of these things still all going on, Jo?

Another aspect of melatonin's chronobiotic activities is the possibility of helping night shift workers to sleep during the day. As a result of the jet lag publicity the Guildford Police (Mark Clarke) approached me to see if we were interested in doing a study of this sort on their sleep and alertness. I asked Simon Folkard to help as he is an expert on shift work, and we carefully timed melatonin (in a comparison with baseline and placebo) to delay their circadian system to improve daytime sleep. I think we were lucky with the schedule timing - as their sleep did improve. On other schedules results from some others have been mixed, and a lot depends on bright light exposure at times which conflict with the circadian shift. Nevertheless, I think that some shift workers do use it if they have access to it and if they find it helps. Simon was also instrumental in stimulating a collaboration with Rutger Wever at the Max Planck Institute in Munich, where I also learnt a lot about the circadian system.

Possibly the most successful therapeutic use of melatonin to date is the treatment of delayed sleep phase, when an individual cannot sleep before the early hours of the morning and then cannot get up at a reasonable time. Professor David Parkes from KCL [King's College London] rang up about this time (late 1980s) to propose a collaborative study on his delayed sleep phase patients. This was a timed treatment with melatonin *versus* placebo and was carried out at KCL with some success, and appeared in *The Lancet* in 1990 - another first. Quite recently a meta-analysis of all the delayed sleep phase studies with melatonin concluded that there is good evidence for efficacy.

Also about this time I was approached by Barbara Stone, a sleep expert working at what was then DERA (Defence Evaluation Research Agency) and is now Qinetiq. She had a background in circadian rhythms having previously worked with Jim Waterhouse and Dave Minors in Manchester, and wished to collaborate. The remit was to ask and answer some fundamental questions related to melatonin, which might also have practical implications. For several years we had wonderful funding, access to an "isolation" unit where

volunteers could be studied in a time-free environment conducive to free-running circadian rhythms, and great equipment. In fact, the unit was set up especially for our experiments. Benita Middleton carried out her PhD work with me in these facilities and we were able to show that melatonin could indeed entrain human circadian rhythms in sighted people. We could also dispel some myths: it was thought at the time that a knowledge of clock time was a powerful time cue for synchronising our rhythms and that if several people were put in a closed unit together that they would synchronise with each other. In fact, we had for each experiment six volunteer soldiers in the same room for up to a month. They had a clock, and so knew what the time was. But they had no natural light dark cycle - the lights were initially kept very dim (less than seven lux). We used our melatonin metabolite assay, rectal temperature, actigraphic sleep and logs to follow the results of different light conditions. In very dim light the subjects free-ran each with a different period in spite of the clock, and we could derive an average free-running period close to the one acceptable today (depends on conditions). We could synchronise them to 24 hours with melatonin, but that is some conditions it could cause fragmented sleep, and we found that it was necessary to provide a light environment (full photoperiod) with around 1,000 lux in order to maintain a 24 hour period in these conditions. I have to take my hat off to Benita for carrying out a large number of such experiments which often involved overnight supervision of the unit, and imposing good compliance, as well as doing huge amounts of analysis. We did all take a turn at the overnights. They are inevitable in all human circadian rhythm research in my experience.

We did a lot of work with Barbara and her colleagues. Eventually, the MoD [Ministry of Defence] decided to build a state-of-the-art sleep lab, and let our little unit go. We then had access in the 2000s to the new sleep unit for some beautiful work by my post-doc Shantha Rajaratnam (now Prof. at Monash) with Benita, defining the immediate and phase shifting effects of melatonin on sleep and the phase shifting effects on a number of other prominent rhythms. These last experiments involved a collaboration with Derk-Jan Dijk who I had recruited for his sleep expertise from Harvard. He is now Professor and Head of the Surrey Sleep Research Unit, and works extensively with our molecular biologists.

TT: So you're still, you're involved with clinical work with the human condition, you're involved with the sheep work, you're involved with, still with the Antarctic?

JA: Oh, all the way through. There were years when I didn't do it, but most years between 1984 and 2012, I gave the base doctor a project.

TT: And how often did you go?

JA: Twice.

TT: I did find one blog piece of yours.

JA: Oh, it's the Shackleton Diary, yes. This is about an American lady. Her boss had sent her in recognition of her sterling work on a trip to Antarctica. She fell over in the tussock grass in South Georgia, which is really quite easy to do, broke her ankle, and she was on a Russian ship which didn't have any morphine or any decent painkillers.

TT: They wouldn't. No, not a Russian ship.

JA: Yes. I didn't know this was true of Russian ships until this happened. And we happened to be in the harbour in South Georgia when this Russian cruise ship turned up and said, 'Would you please take this lady and do something with her?' It took six guys to carry her down the gangplank, but mind you it takes six to carry a coffin, doesn't it?

TT: Oh dear.

JA: No, it's alright, she survived. And she arrived in the middle of the night on our ship, which was the RRS

Shackleton, and the captain was absolutely incensed with this. I can see him there striding around in his pyjamas saying absolutely unprintable things about the Russians.

Anyway, so she landed with us and was given suitable treatment and strapped up. We had already got one broken leg on board. On arriving on the base, the first thing the new base doctor had to do was deal with somebody who had broken their leg skiing behind a Ski-Doo, you know, they tow them around. This would be 2000-2001.

TT: So this was your first or your second time?

JA: It was the first time.

TT: Did you actually do field work yourself when you went out there? Were you actually supervising some of the research?

JA: Well, I was the Medical Research Supervisor from wherever I was. What I did there, was a bit of psychological questioning on request, the British Antarctic Survey wanted to see who would cope with the situation better than others. They called it SOAP, Selection of Antarctic Personnel - this project went on for several years. And they asked me if I would do the questionnaire with all the various people at Halley that year. Mostly it was very important for me to appreciate the actual conditions down there, and how we could change the light conditions for the better as this was to be the focus of the future projects. I also took these potential UV [ultraviolet] monitors out with me, because I had this silly thought about personal monitoring of exposure to different spectra of light. I'm digressing but, sorry do you want me to shut up?

TT: No, no, no, please carry on.

JA: Because we'd been involved in the effects on melatonin of different spectral composition of light and that came into your text. We'd been messing around with it for several years in fact. Jim Horne, a sleep researcher from Loughborough, and I published some effects of green light as compared to white light in the mid-1990s. And Debra (my colleague Professor Debra Skene) had looked at colour-blind people and the effects of light on their melatonin to see if we could pick anything out of the spectrum there. And then Russell Foster came into the picture.

I knew Russell (Foster) when he was a PhD-student. He was doing optical fibre work, putting light directly into birds brains. And he came over with requests for some advice on this, that and the other. Anyway, when he got back from America he said, 'Can we put in a joint grant application?' I think because he'd been told that he really ought to have some human work in with his grant applications, and so he and I and some others from Europe put in for a European programme grant to look at an action spectrum of light on melatonin suppression n humans as well as what Russell was doing in his retinally degenerate rats and mice. Rob Lucas was involved in all of this at the time. I'm talking now 1999. And it was, you know, it was a big grant, and we got it, and Debra was the lead person, as I said, on our end of it. She and I had a joint PhD-student (Kavitha Thapan) who did the action spectrum in humans, very tedious thing to do for a PhD, but she did it beautifully. And it was published the same day as the nearly identical George Brainard one in America.

Russell in the meantime had these two *Science* papers in 1999 showing that, even without a functioning retina, mice could respond by circadian shifts to light and by melatonin suppression. And that was the intrinsically light sensitive retinal ganglion cells and the melanopsin photoreceptor, so important for resetting the circadian clock, underlining the importance of blue light at *ca* 480 nm. So we were all involved in this together.

And, as I said in the text [see Overy and Tansey (2014)], my first thought was, 'Well, they do have delayed sleep in Antarctica in the winter and they have low mood. They don't have SAD, but they do have low mood, because the American base at McMurdo has published that they have low mood, and we should do

something about their light conditions to correct circadian phase, improve sleep, and improve mood.' And this is years after that original 1984/5 phase shift with the skeleton light. And on this occasion Phillips lighting were very helpful, because the first year we did it, they supplied 35 light boxes giving 10,000 K blue enriched light. And they paid to ship them down there. And then they upped the Kelvin to 17,000, which was much brighter and bluer, and we did a second experiment. So onward two years, and I went down South again for both those projects, and also to do a sleep study on the ship's crew.

What I did was to design the protocol with the base doctor, mostly by e-mail in fact, on both occasions. Vicky Mottram was the second base doctor, Gavin Francis the first. They came to the lab, we met, we explained what we do, we gave them loads of stuff to read and said, 'Look, this is what we want you to do.' It has been said to me, 'Well, this is all nonsense, isn't it, this light treatment of people for SAD?' And we said, 'Well, delayed phase and poor sleep is not SAD, but it's related. So you know, get out there and give them some extra light.' We did a particular protocol right through six months with a month's blue, a month's white, a month's blue, a month's white, a month's blue, a month's white. And it was symmetrical so we got the same photoperiods with blue and with white. And the first lot of blue light (10,000 K) was not very effective.

The maximum lux with the existing base lighting we could measure down there, in 1985 and in 2000 was about 500 lux. And if we sat by your window today, we'd probably get 1,000 or so. It's standard indoor lighting, but of course, there's no outdoor sunshine in the winter to back it up. With the first 1985 study, we made sure they got 2,000 lux for an hour, morning and evening. But trying out the blue-enriched *versus* white light, we decided it was easier for them to put the lights all-round the base, have one by each bedside and in the work rooms and in the garage, and Phillips supplied us enough lights to be able to do that, and for us to have them on all day. So they got pretty much a full photoperiod, 10-12 hours' worth say, and we told them to turn them off at six o'clock in the evening. Well, you could see on the records actually, because the actigraphs measure light exposure as well as activity and sleep (they can measure lots of other things as well). When they experienced up to 1,000 lux in 24 hours, and it could be any time during the 24 hours, it had a minor effect on sleep efficiency. And it had a minor effect on shifting the delayed phase to a slightly earlier time. But the second study down there with blue-enriched *versus* white light, they had 17,000 K blue light, which Phillips call ActiViva Active, and this time we had highly significant improvements in sleep in timing in particular, in sleep efficiency and a significant advance shift in circadian phase.

On that occasion they got 2,000 lux maximum similar for both types of light. And there was very little difference between the treatment of the blue enriched and the white light. Now if you were to say, as I believe Harvard have done, if you just take the blue wavelengths in that blue light and give them just the blue, you wouldn't need anything like so much light. And that's quite possible, and so when I say that the blue was no more effective than the white, I'm meaning blue mixed with white, and not corrected for wavelength energy, because there's more energy in blue light. But it was significantly better, both blue and white were significantly better at improving sleep, improving circadian phase *etc.* But as you saw from the text and people's discussion [see Overy and Tansey (2014)], nobody yet has shown convincingly in SAD that one is better than the other, I'm afraid. One of the things we did with Stuart (Checkley, at the Maudsley) a long time ago, was to look at the effect of three hours of light *versus* one hour of light, morning and evening on melatonin, and there was no difference really in the effect on melatonin. Chris Thompson found some evidence for changes in sensitivity to light in SAD as is discussed in your text [see Overy and Tansey (2014)].

TT: Throughout this period, Jo, because the last time we talked about this you were an experimental officer, which was in, this is the late 1970s, early 1980s, when you…

JA: Very early 1980s, yes, so late 1970s, and 1980. Then I had this op and I was off for about six months. And I wasn't too hopeful, one thinks, 'Oh, how long have I got?' But I said, 'I want to come back, Vincent.' And it just so happened that he had a part-time Senior Lecturer leave at that time, and that post became available, and I got it with a full board interview, as part-time. Don't quote me on this, I was told, 'Well, you don't need a full-time job, you've got a husband.'

TT: Been there, yes, had that myself, yes.

JA: Extraordinary.

TT: At about the same period, yes.

JA: The kids these days, they can't believe it. Anyway, yes, oh that was when the Wellcome must have taken over to give me a decent salary because I think it was two fifths, the Senior Lectureship. And I think they must have given me a salary for several years on condition the University gave me a full-time job at the end of it, which actually they never did. I never had a full-time job there ever since. At some point, I took early retirement on condition that what existed of my post was used for a Lectureship for my research group, and I went back on contract. The first Lecturer was my ex PhD-student Stephen Deacon who did not stay very long, and then the molecular biologist Malcom von Schantz - to bring molecular biology to the group.

TT: So you've always been officially a part-time?

JA: Yes. Since the Experimental Officer post. Well, it had its ups as well as its downs. I could do what I liked in my own time.

TT: When you say your own time, so you could get research grants in your own time? Surrey would still allow you to use facilities?

JA: No, if I applied for a formal research grant, which, of course, we did lots of the time; that was through the University of Surrey.

TT: And that was your two fifths or your part-time?

JA: That would be what I was working on but I did a fair bit of teaching as well. I set up and ran final year modules in Biological Rhythms and in Neuroendocrinology. What we did with Stockgrand Ltd, the company I set up in 1988, we would take on selling reagents, doing the assays for money, and every so often, it doesn't happen now though, because then the pharmaceutical companies were interested in melatonin, we would do a pharmaceutical company project, we'd make a profit and we'd use the profit for research support. I didn't really take a salary from it, to tell you the truth, but a small annual bonus, conferences and all of that sort of thing. I got a Chair in 1989, I think perhaps officially in 1990.

TT: So that was still part-time?

JA: Yes.

TT: So throughout, you said at one point, when you were talking about Geneva, mention these three F's, the foreign female with family. Do you think that if you had been a man you would have been supported more? Would you have had a full-time job?

JA: Very likely, yes. I had to give a talk to the European Sleep Research Society in Lisbon a few of years ago on women's experiences in sleep research. I suppose I could say I've done quite a bit of sleep research, even though I'm not a sleep researcher. And I found the most extraordinary figures from UNESCO. The figures for women entering, say, science and technology and medicine, they are more than 50% for university entry level. And at the other end of the scale, at Chair and better than Chair level, it's less than 10%. Not fair.

TT: And that's an improvement from what it used to be. I want to ask you about influences in your career. You've mentioned a few names as we've gone through. So influences, both good and bad

JA: I'll tell you who I have greatly admired and that's Joe Herbert in Cambridge. Lovely man.

TT: What in particular about Joe Herbert?

JA: Just the way he thinks. And I have enormous admiration for Gerald Lincoln. He's a real gentleman, and just to listen to him talk about science is a pleasure. He's terrific.

TT: And why, what is it? Is it the breadth, the depth?

JA: The depth and the sort of comprehensive understanding of the entire subject. In fact, Gerald was one of our entries into sheep photoperiodism because in 1979ish he worked on Soay sheep, which come from the island of Soay, and he ganglionectomised them. This is done to see what the pineal does as its principal innervation is from the superior cervical ganglion. (Joe Herbert and Klaus Hoffman in Munich at the Max Planck, had done pinealectomy prior to this. In the case of Joe it was ferrets, and in the case of Hoffman it was hamsters; to see what effect it had on their seasonal breeding. And it did have an effect. They ceased to time it correctly). Gerald did it slightly differently in Soay sheep. He took away the pineal principal innervation by superior cervical ganglionectomy, and he wanted to know if they produced any melatonin after that. So that's when he got in touch with me and said, 'Would you like to measure melatonin in my Soay sheep?' And, of course, I did. And that was published in, ooh, I think 1981, something like that. And the melatonin profiles were flat, no rhythm in the ganglionectomised sheep. It was another very nice, sort of validation of our assay as well. And we then pinealectomised our own sheep, got the local vet to do it, and they had a completely flat rhythm down in Surrey, they were Suffolk Cross ewes, they weren't Soays. And that I presented at the Endocrine Society, but we never, ever wrote it up as a full paper, which was silly. I mean there's lots of things one regrets not publishing as full papers. But then, sort of life moves on and you want to do something else, and it's more exciting and anyway, it was pretty obvious to me. I thought if you pinealectomise a sheep it gets rid of its melatonin. But it's there as an abstract, a published abstract, and refereed.

TT: And can I just ask about meetings, conferences, because you've mentioned a few. What was the most important society as far as you were concerned, or did it change through your career?

JA: Well, the Gordon [Research] Conference introduction was enormously important. I've been to every pineal Gordon Conference bar one, and they've just stopped having pineal Gordon Conferences, which shows you that the pineal is still very much a niche, but not melatonin. This now goes in the sleep Conferences and to some extent in the chronobiology Conferences. But yes, the Endocrine Society was very important. And Brian Pickering (former Deputy Vice-Chancellor of the University of Bristol) introduced me (I think), to the Society for the Study of Fertility over here, and that was very important (we met in Geneva). I did the Hammond Lecture for them one year on our sheep, of course. We did quite a lot on sheep really. And there was a commercial aspect as well, which I can get back to. But the one which is closest to my heart, although perhaps not so much these days, started off as the European Pineal Study Group in 1977. And I and the Founder and Helena Illnerova - who was President of the Czech Academy of Sciences - we've just written the history of this little Society as we see it, briefly, in the hope that somebody might read it. Anyway, it's on the web. It's called the European Biological Rhythm Society now.

TT: And were you a Founder Member of that?

JA: Yes. And I was President for three years, I think. Yes.

TT: And what was your purpose in starting that? The obvious answer is because there wasn't anyone else addressing those issues.

JA: That's right.

TT: But there must have been a nucleus of people, a core of people you wanted to talk to?

JA: I wasn't quite as much a Founder as all that. I was certainly a Founding Member. But the actual Founders

were Professor Johannes Ariens Kappers, Head of the Brain Research Institute in Amsterdam, who found the sympathetic innervation of the pineal. And his student, now Professor Paul Pevet (now in France Strasbourg). Kappers and Paul wrote to all the people they knew who were interested in the pineal in 1977 and we met in 1977 in Jerusalem at a pineal conference organised by a chap called Isaac Nir, who has got quite a lot to do with WHO [World Health Organization]. And they asked if there was interest in forming a society to study the pineal gland. I think they got around 180 replies which was enough to set up a society, and it met in Amsterdam for the first time in 1978 [sighs]. Happy days. Sorry, I do get overcome by nostalgia sometimes, because it was such fun right at the beginning. And it has been very important to anybody involved with the pineal, and with melatonin for a while, for a long while in fact. But when it became obvious that the importance of melatonin is to do with the whole circadian system, it evolved, and whilst I was president I changed its name to the European Pineal Society, and then suggested that it become the European Pineal and Biological Rhythms Society, and then finally in Frankfurt in 2005, it became the European Biological Rhythms Society, which is where it is now. Russell was President three years ago, I think. Prof Till Roenneberg is President at the moment and my successor, Prof. Debra Skene, is going to be President next. And we're meeting in Manchester in August.

TT: Would you like to talk about shift work and some of the other human studies?

JA: The shift work has been pretty important for me.

TT: How did you get started with that?

JA: Well, I was rung up by Mike Forbes, the occupational health doctor of a large oil company, and he said, 'I'm a bit worried about accidents on the night shift.' And he said, 'I have got a little bit of money, would you like to do some investigations?'

TT: And when was this?

JA: Probably 1995. And it's not often, you know, that a project just falls into your lap like that, although I must admit I was also once rung up by the National Grid and was asked if I would like to do a project on electromagnetic radiation and melatonin. So we didn't say no to that either. My post-doc Guy Warman (now in Auckland) and a PhD-student Hayley Tripp, carried out the studies - which showed no effects using our specific protocol.

Anyway, shift work: yes, Mike Forbes said he would perhaps have enough money to support a PhD-student. So I engaged a chap called Richard Barnes who had done his degree at Surrey, and sent him out to collect samples of pee and records of sleep and photo period on the rigs to which we had access, which were the Shell rigs at the time. Tern is one and Sedco another; both at around 62^{o}N. This is all published. I did a little review with a post-doc (Rajaratnam) in *The Lancet* on this, and for *Occupational Medicine*.

Richard measured what happens to the circadian system of a shift worker on day shift and night shift in different types of shift schedules in the North Sea. This is a very particular situation, because they have no social life. Once they finish work, you know, they can watch a film, go to bed, there's no alcohol, it's all men, although I think some of the cleaners might be women. And what we wanted to know was if the circadian system adapts to nightshift in these circumstances. They're out there for sometimes three weeks. Because if you are not adapted, you are trying to work under par in a relatively dangerous environment. We wanted to know if there was an explanation for nightshift accidents on nightshift, because the circadian system is desynchronised, *i.e.* not fully-adapted. If you are not adapted you are trying to sleep at your most alert phase, and you're trying to work at your least alert phase. And the way we did it was using this wonderful melatonin metabolite assay in urine (developed in the 1980s by another PhD-student, Chris Bojkowski), which reflects melatonin production, and therefore reflects the internal clock activity, and the circadian status of the people. And Richard went out there and collected pee, sequential urines for 24 hours, every day that the guys were out there. So a fortnight worth's of urines, which is good data, it's really convincing data.

TT: Well, you mentioned that earlier and one of the things is, one of the things we're always interested in with our Witness Seminars and with these interviews, is getting behind the published papers. So can you just say something about how that was all negotiated and set up? He/she arrives there with lots of canisters, plastic bags, deep freezers, all that kind of facilities. I mean was it already explained to all the participants, did he/she then have to start negotiating individually?

JA: Richard led the charge with the help of the rig paramedics and talks to the guys to explain what he was doing and why they should volunteer. He was succeeded by a young woman (Michelle Gibbs), whom I can talk about as well. It was not as difficult as you might imagine, because you only need somebody to measure the urine volume each time they pee, and they're perfectly capable of doing it themselves in fact. If they're compliant, they record volume and the time and keep a tiny little bit in a pre-labelled tube. Because we can measure it on, well 0.1 ml or less. We dilute the urine before we actually measure it. So we don't need very much. Once it's collected and recorded it needs very little storage space, it goes into a deep freeze. The measuring cylinder and the urine collection bottles are carefully washed out and used for the next time, and no preservative is needed for a short time as the metabolite 6-sulphatoxymelatonin is rather robust. So you only need one collection set per person. We have persuaded many blind people to do sequential urine collections using speaking scales for urine volume, and Braille-labelled tubes for sample storage and audio tapes for keeping volume, time, *etc* records. I've also done this on ships' crew working shifts sometimes in a force ten gale, and the crew are perfectly capable of doing that as well.

TT: So somebody was out there for how long? Two weeks?

JA: Initially to set up the experiment and explain to the guys how to do it and how it was important. They didn't stay out there the whole time or go every time. The paramedics were very helpful on the rigs. Once a paramedic knew what they were doing, they could get through it all by themselves and send urine and records back to Guildford. That was not a problem. But both of them, both of these PhD-students went out there to start with to explain things, and I was told I ought to be going out there, but I was sixty something by then, and I didn't particularly want to, I'm afraid. I didn't really have time. Okay, I was a coward. You have to be able to get out from an upside down helicopter in a swimming pool in order to be allowed to go out there. I just didn't think I could cope.

TT: And were there psychological tests and activity monitors as well?

JA: Good question. We did sleep records with activity when they paid for us to have some actigraphs because they were not cheap. They were £800 a piece at the time. The first experiments that the young man did were simply collecting the urine and recording the timing of sleep, and what the photo period was because that was always of interest. We didn't have the objective sleep monitors at that time, but we have since. Richard got some very nice data, because he showed very clearly that certain schedules, if you're working six in the evening to six in the morning, that's the eighteen six night schedule, they adapt, not quite everybody but most people. The whole circadian rhythm shifts by nearly 12 hours to be in the right phase to be working at night and being awake during the day. And this is almost completely unknown in shift work on shore. Night, even permanent nightshift workers, hardly ever completely adapt. There's a review on that by Simon Folkard of shift work studies which used 6-sulphatoxymelatonin - the metabolite we use to show where the clock is. But if you were on the schedule which runs from midnight, 24:00 to 12:00 (nightshift) and 12:00 to 24:00 (day shift), you don't adapt. And this is to do with the way that they are exposed to light on this particular timing at a time, which stops the circadian system adapting. It's absolutely crystal clear how this works.

And so whether you're in work mode when you're supposed to be working or not, depends on the schedule that you're working. There were other schedules that we looked at: the so-called "rollover shift", which Katherine Parkes has studied in great detail, and she showed first that the rollover shifts were poor for sleep and alertness and performance. We then came along and looked at the circadian status of rollover shifts and they are absolutely horrendous really. There's a seven nights' then seven days' shift (18:00 to 06:00, 06:00 to

18:00) which is the worst from a circadian point of view, because in a week they nearly all, well most of them will adapt to the nights and then they've got to go back again to days. So they spend the whole time out there, nearly all the time, desynchronised. But anecdotally, they think it's great, because they reckon they're more in sync with home time when they get home than on the 14 day, 14 night shifts. Because if you have fully-adapted as they do to the 18:00 to 06:00 night shift, and you're 12 hours out of phase when you go home, you have a terrible time for the first few days.

TT: And what was the impact of that work? Did it actually alter the work schedules?

JA: Well, there's a little intermediate story to tell you in between, because somehow probably in an Aberdeen pub, the rumour grew that Shell were feeding their oil rig workers melatonin to make them more productive. And they instantly stopped the project. And they employed a Professor of Risk Assessment to see if our little project was a major problem for this gigantic, multinational oil company. And so, poor old Richard, he got some very nice field data, but we then had to simulate shift work in the lab for him to complete his PhD. But the Health and Safety Executive heard about this and they said, 'Well, we think it's quite important - this work. We'll fund it from now on.' And they did. We had the best part of ten years funding from the HSE [Health and Safety Executive] to look at different schedules in the North Sea, and actually off Morecambe Bay and the East coast as well. And based on the fact that people are theoretically healthier and sleeping well when they fully adapt, it was recommended that people work the adapted schedules. However, the last I heard, was that this was very unpopular.

I haven't actually looked up the situation for a while. The last project went out, oh, it must have been 2008, and was written up. There's a whole account of all these studies by Michelle Gibbs, the student that completed the studies out on the oil rigs. She wrote a huge report for the HSE, which is publicly available, and she recommended that they should change the shift schedule timing to three in the morning to three in the afternoon, being the day schedule, and three in the afternoon to three in the morning being the night schedule, because it's easier to shift a little bit in one direction to sleep on one of those and in the other direction to sleep on the other one. I thought that was a jolly good idea, but I don't know if anybody's actually taken it up.

We did one more field project after that which was - let me think - I think it was funded by Stockgrand, but I'm not absolutely certain, in which, because they have such a hard time after being adapted on the rigs when they go home, we said, 'Well, let's see what happens to them when they're at home, and if we can give them some light at the right time to adapt them back to home time.' And it was really hard to do. That was another PhD-student, Helen Thorne. Because once they had escaped, you know, it's hard to get good compliance. But we got some evidence that light was quite effective.

We also did a number of simulated shift work studies at Surrey with other PhD-students in which we were able to show that eating on the unadapted night shift leads to an increase in risk factors for cardiovascular disease, diabetes and metabolic syndrome. These were collaborative with my colleague Linda Morgan who was Professor in the Nutrition Department at the time, and Dr Shelagh Hampton. In particular, we were able to show an increase in triglycerides and evidence of insulin resistance after a night shift compared to a day shift meal. Both metabolic studies on the oil rigs (Michelle Gibbs) and our field study in Antarctica (Jon Lund) showed clearly that these phenomena were present in real shift workers. They are due to disruption of the major circadian aspects of metabolism, and this line of research is being vigorously pursued at present at Surrey and elsewhere, largely *via* a molecular biology approach. The health risks of shift work (increased risk of cardiovascular disease, certain cancers, diabetes, metabolic syndrome) and the "obesity epidemic" underline the importance of this area.

TT: You're now retired, but like most academics you're still busy working. Are you still involved in any lab research or are you mainly a Consultant?

JA: I don't do anything to interfere with Debra's research. I kept well out of the way. I think it must be awful to have, you know, your old boss breathing down your neck. What I've been involved in has been mainly

consultancy but mostly to do with interesting projects with the Canadian Military in Toronto and in the Canadian Arctic. The British Antarctic Survey decided in 2012 they didn't particularly want any more medical projects of the kind that I did at the new Halley, and that was a shame because I would have been happy to go on doing it. As a result of our highlighting light in that environment in winter, the lighting architect for the new base, which is only two or three years old now, came to see me and said, 'What about all these circadian actions of light?' I can't tell you how delighted I was that it had a practical outcome in the design of lighting for the new base. Because you know it really is important light, and I can't emphasise how important it is enough. What I would have liked to do, of course, would have been to look at sleep, mood and circadian phase on the new Base with the new lighting, but it is not to be.

TT: And what are you doing in the Arctic?

JA: Yes, that's interesting. The Canadians want, well, first of all the Canadian Military Research Group in Toronto (Michel Paul), asked if I would consult over the use of melatonin in jet lag - they were concerned about the deployment to Afghanistan *etc.* And they wanted to do some of their own experiments to see if it would help people shift, and it did, and that was three or four years' work, in fact. And then after finishing that, which is now published, all of it, they said, well, they want to deploy people into the Arctic, many more than are currently there, I believe mostly for Canadian territorial rights over no doubt things that lie under the sea, like oil. And they want to put a lot of people out there because Russia and Denmark also have territorial claims. And they want to take care of their health while they're out there so they want to know, first of all, what happens to the circadian systems, at 83^{o}N and thereabouts. Halley was only 75^{o}S, but this is pretty far north. And if, as expected, you get problems like delayed phase, they want to try treating them with light and melatonin. So it was right up my street this project; I loved to be involved in that. And I've spent quite a lot of time on it.

TT: Can I just ask you, I was just thinking as you were talking, has anybody looked at, say, native Indians and the Inuit and circadian rhythms?

JA: Well, I had to avoid that. I've written a review of biological rhythms during residence in the polar regions, in which I deliberately excluded all of the native work. There was a very famous English physiologist called Mary Lobban who did rhythms in Svalbard years ago in the 1960s. And she showed that the native people, people who live there all the time, were rather different from ones that came in and stayed a while and then went. And there was enough to write about on the temporary residents. It's a really interesting area for me, partly because there's so much interest in the oil reserves up there. I had a Russian approach me to say that there were terrible problems in the Russian Arctic workers; a lot of Russian oil comes from the Arctic and is syphoned down to Europe, as I'm sure you know. And could he come and work with me on it. And I said, 'Well,' - this is two years ago - 'I'll have to find some money.' And we applied for money, but we didn't get it unfortunately. I expect I was too old. If you look up the literature you can see that they have much-increased incidences of cardiovascular disease, for example, and sleep problems compared to Western European workers.

I should just mention that I did a couple of sabbaticals in France at INRA [Institut National de la Recherche Agronomique], Tours, doing sheep work with Jean-Paul Ravault, and one in Canada with (Prof.) Greg Brown at McMaster University in Ontario looking at individual differences in sensitivity to melatonin suppression by light. They were enriching and fun.

TT: Thank you so much.

[END OF TRANSCRIPT]

Further related resources:

1. Overy C, Tansey E M (eds) (2014) *The Recent History of Seasonal Affective Disorder (SAD).* Wellcome Witnesses to Contemporary Medicine, vol. 51. London: Queen Mary, University of London.

2. Tansey E M (intvr); Tansey E M (ed) (2017) *Arendt, Josephine: transcript of a video interview (17-Mar-2015)*. History of Modern Biomedicine Interviews (Digital Collection), item e2017154. London: Queen Mary University of London.