Parkinson-Alzheimer interview (part 2)

Question 1 from Alois Alzheimer: with regard to my disease, named Alzheimer, what happens exactly? The hippocampus is associated with the memory, what is its volume, and can it increase or decrease?

Dear Alois Alzheimer, in the disease that bears your name, the secretions of the 3 pineal hormones, Melatonin (which protects the neurons), 6-Methoxyharmalan (the wake and cognition hormone) and Valentonin (sleep and night-time hormone) break down, which is perfectly correlated with the clinical symptoms of the disease.

This is clearly explained in Letter no. 138 from Pr Henri Joyeux of 18 October 2016 : "Alois Alzheimer's incredible letter about the discovery of Sleep-Wake regulation", and the video: *Les causes et le traitement de la maladie d'Alzheimer enfin découverts !* (The causes and treatment of Alzheimer's disease finally discovered) by Professors J.B. Fourtillan and H. Joyeux (YouTube: duration 13 min 30)

While the hippocampus is considered the memory area, the physiological mechanism of this event backup process is totally unknown: short, medium and long-term memory.

Its volume is generally around 3 to 3.5cm^3 in adults. By comparison, the volume of the cerebral cortex is 320 to 420cm^3. In the disease named after you, Alois, the volume of the two hippocampi in the centre of the brain decreases and, conversely, can reach 4cm^3 when memory is strongly stimulated.

In the disease that bears your name, the reduction in physiological sleep time and in the duration of the corresponding REM sleep is correlated with the patients' memory loss.

More specifically, the reduction in REM sleep(1), induced by hypnotic drugs, benzodiazepines and related drugs (Zolpidem, Zopiclone), is correlated with the amnesic effects, therefore the memory loss, of these drugs.

In the terminal stage of the disease, the brain volume can decrease by up to 30 percent, which corresponds with a significant destruction of the nerve cells.

The administration of a replacement treatment by the 3 hormones of the Sleep-Wake system, with the oral ingestion of 3mg of Melatonin, and the transdermal administration of a combination of Valentonin and 6-Methoxyharmalan, in the form of a patch, should help restore the patients' memory and mental functions, provided they are not too deteriorated.

The treatment must of course be provided before the terminal stage of the disease, i.e. as soon as possible, upon appearance of the sleep disorders, whether or not associated with impaired senses of smell and taste. This will help avoid sleeping pills, anti-anxiety and anti-depressant drugs which, as is now demonstrated, ultimately increase the risk of Alzheimer's by 50%.
It would therefore be foolish to envisage, at an advanced stage of the disease, the reconstruction of

neuronal tissue and, even more so, the increase in the volume of the hippocampus.

Question 2 from James Parkinson: in my disease, known as "Parkinson's", where are the brain lesions? And why does the electric current struggle to reach the limbs, which start shaking or stiffening, preventing patients from walking normally?

In patients suffering from the disease named after you, James, there is a destruction of the neurons which produce dopamine, known as dopaminergic neurons. These neurons are located in nuclei in the centre of the brain, in the *substantia nigra* of the *Locus niger* and the striated ganglia, called *Striatum*.

Nerve impulses are transmitted in these neurons by a well-known neurotransmitter, dopamine. As dopamine is synthesised in the pre-synaptic endings (2) of the neurons of the aforementioned nuclei in the centre of the brain, their destruction reduces the amount of dopamine available.

Therefore the downstream nerve transmission towards the neuromuscular connections is disrupted, notably affecting muscle flexibility and relaxation, hence the motor impairments in Parkinson's patients, tremors and muscular tension.

As with Alzheimer's disease, Parkinson's disease and Parkinsonian syndromes are due to a largely insufficient secretion of the 3 hormones produced by the pineal gland (3) (Melatonin, MLT, 6-Methoxyharmalan, 6-MH, and Valentonin, VLT) which manage the Sleep-Wake system.

To understand the origin of the disease named after you, James, the role of the two hormones, Valentonin (VLT) and 6-Methoxyharmalan (6-MH), on the tone of the muscle fibres in the entire body should be reiterated.

When the body is in sleep mode, the VLT hormone causes rest-related muscle relaxation, via the specific allosteric activation of the D1 and D2 dopaminergic receptors of the basal ganglia. This is what I explained in detail in your previous interview, and I know how difficult it can be to understand, except for my biochemist colleagues, to whom I give my regards.

Conversely, during the day, the 6-MH hormone causes the contraction of muscle fibres, which enable the normal functioning by antagonism of these receptors.

These actions of VLT and 6-MH are explained in the video: "The Sleep-Wake system in Creation" by Pr J.B. Fourtillan (YouTube, duration: 14min 35s + 2min 13s)

The discovery of the Sleep-Wake system therefore sheds light on the origin of these movement disorders. During the night, when the body is in sleep mode, VLT increases, by allosteric deformation, the sensitivity to dopamine of the D1 and D2 dopaminergic receptors, which causes muscle relaxation.
VLT acts as a dopaminergic agonist, i.e. a substance capable of reproducing the effects of dopamine on its receptors. This is therefore the logical substitution treatment for the disease named after you, James.
What differentiates it however from the current treatments proposed to patients from the onset of the disease, Levodopa (4) and antiparkinsonian dopaminergic agonists (Apomorphine, Pergolide, Pramipexole,

Ropinirole, Rotigotine, etc.), is that, firstly, VLT only activates the D1 and D2 receptors in the basal ganglia and, more importantly, it only acts during the night, when it is prevalent in the body, in comparison with 6-MH. It promotes restorative sleep and puts all voluntary muscles into sleep mode.

However, when Levodopa is used in tablet form, it is absorbed by the digestive tract and travels through the bloodstream to cross the blood-brain barrier. It increases the quantity of dopamine in the dopaminergic receptors of the basal ganglia and activates these receptors 24 hours a day, as is the case with antiparkinsonian dopaminergic agonists, by causing permanent muscle relaxation, when this relaxation should be limited to the nocturnal rest period. This makes the daytime phase even harder to bear.

The therapeutic failure of existing antiparkinsonian medications result from the fact that they do not treat the muscle contraction disorders during the day, due to the insufficient production of 6-MH by the pineal gland.

When we wake up, 6-MH is what reactivates the muscular system.
In other words, only part of the disease is treated, muscle relaxation, and the patients suffer from the side effects of somnolence and high blood pressure, due to dopaminergic stimulation during the day.

All this is explained in Letter no. 139 from Pr Henri Joyeux of 09 November 2016: " ", and the video: *Les véritables Causes et le traitement de la maladie de Parkinson* (The real causes and treatment of Parkinson's disease) by Professors J.B. Fourtillan and H. Joyeux (YouTube: duration 14 min 25)

Question 3 from Alois and James to Jean-Bernard Fourtillan: you have noticed how poorly our Alzheimer's or Parkinson's patients sleep. Sometimes they have negative thoughts going round in their head... waking them up in the middle of the night.

In Alzheimer's and Parkinson's diseases, the insufficient secretions of the 3 hormones of the Sleep-Wake system, particularly Valentonin, the sleep hormone, exposes patients to insomnia and nervous breakdowns. And of course, being diagnosed with the disease can have a negative effect on patients, leading to depression.

Question 4. Why do sleeping pills make them so groggy, to such an extent that they lose their memory? Chemical sleep does not work; why is not really restful?

"Groggy" (or numbed, knocked out) is a good term to describe the harmful and deleterious effects of sleeping pills, benzodiazepines and related drugs (Zolpidem, Zopiclone), on patients.
They ensure "anaesthetic", non-restorative sleep for the body, and are responsible for amnesic effects (anterograde amnesia: loss of memory of recent events).

Conversely, VLT ensures restorative physiological sleep characterised, on an electroencephalogram, by an abundance of deep, restful sleep and REM sleep necessary for the memory.
In addition, these sleeping pills-hypnotic drugs fail to live up to their name as their adverse effects are what prevails in patients, first and foremost significant insomnia and anxiety, referred to as paradoxical as they are the opposite to the desired effects for which they are taken.

The sleeping pills currently available, i.e. benzodiazepines and related drugs (Zolpidem, Zopiclone), destroy physiological sleep and are therefore ineffective.

The discovery of the Sleep-Wake system helps explain the paradoxical anti-sleep effects of benzodiazepines and related drugs. Their chemical structures feature the pharmacophore model (5) of 6-MH, equivalent with that of LSD, to which they owe their psychostimulant and anxiety-inducing effects, disturbing sleep and potentially causing nervous breakdowns.

It is clear that the discovery of benzodiazepines in the 1950s, and of related drugs subsequently, was not a good thing for the health of patients, who are still prescribed them to a large extent. Obviously, there was nothing else to prescribe.

While they have generated hundreds of thousands of dollars for the pharmaceutical laboratories who placed them on the market, they have caused immense damage without doing much for the patients to whom they are prescribed.

All this is clearly explained in the book and the brochure I wrote, as well as Letter no. 144 from Pr Henri Joyeux accompanied by a video: "Sleep disorders and how to treat them", which will be published one week after this letter.

Question 5. Ultimately what you are doing is very original; informing scientists at the same time as the general public. Why?

The existence and functioning of the Sleep-Wake system, which were clearly revealed to us, and the resulting treatments, are great news for patients suffering from neurological disorders. We will now be able to prevent and treat the diseases you described in the early 19th and 20th centuries.

Along with my friend Pr Henri Joyeux, we decided to inform patients, who are primarily affected by this discovery, at the same time as the general public, healthcare professionals and researchers, with no order of precedence, but for the benefit of all.

You will notice that, for the first time in the history of medicine, physicians will be able to make an informed decision, prescribing a medicinal product to their patients and explaining its purpose and mode of action, i.e. justifying their prescription.

This is a real first!

To be fair to the prescribers, it should be pointed out that, up until now, they were unable to do so as pharmaceutical laboratories provided them with drugs they knew little or nothing about in terms of modes of action.

So much so that, to this day, it is still unclear why aspirin has analgesic, anti-pyretic (it lowers the body temperature in case of fever) and anti-platelet aggregation properties.

Question 6. You intend to give these hormones as a replacement therapy to those who need them in the form of patches, and the hormones will act by cutaneous absorption; why not orally?

To offset the insufficient pineal secretion of the 3 hormones, in neurodegenerative diseases, Melatonin must be taken orally, in the evening at bedtime. It is absorbed through the digestive system and spreads through the bloodstream.

A dual-compartment transdermal patch will be applied simultaneously to deliver Valentonin and 6-MH in the bloodstream during the sleep period, i.e. for approximately 8 hours. This is the only way to introduce these 2 hormones in the bloodstream while reproducing their release patterns by the pineal gland, under physiological conditions, during the night.

The oral route is impossible for Valentonin as it is entirely destroyed in the acidic environment of the stomach. Furthermore, the oral administration of 6-MH and VLT would make it impossible to reproduce the hormones' release patterns, at a constant rate, in the bloodstream by the pineal gland, and to limit the release period to the timeslot between bedtime and waking up in the morning.

Question 7. Why single or dual-compartment patches? For the treatment of neurological disorders due to a shortage of hormonal secretions by the pineal gland, dual-compartment patches must be used, containing VLT and 6-MH separately.

They must be applied in the evening, at bedtime, and removed in the morning upon waking. The hormones will be directly absorbed by the skin.

The idea is to separately control the transdermal passages of the 2 hormones into the bloodstream, in order to release the following into the body during the night (approximately 8 hours):
– either 400 microgrammes of VLT and 100 microgrammes of 6-MH, for the neurodegenerative diseases named after you;
– or 200 microgrammes of VLT and 50 microgrammes of 6-MH, for the treatment of sleep disorders and nervous breakdowns.

For the treatment of psychotic disorders caused by excessive hormonal secretions, single-compartment transdermal patches containing VLT shall be applied between 8am and 12pm, to release a dose equal to 5 microgrammes of Valentonin per hour per kg of body weight into the body.

By working on the competitive binding of VLT and 6-MH, this will help reduce the effects of the excessive concentration of 6-MH on the 5-HT_{2C} serotoninergic receptors, responsible for vigilance.

Question 8. How will patients know they need this treatment?

Patients will have their plasma concentration of Melatonin measured in the middle of the night, from 1am, as this is a quantitative marker of the pineal hormones' secretion.

Patients will therefore determine the secretion capacity of their pineal gland, and the risks they run of suffering from neurodegenerative conditions such as the diseases named after you.

A marker of less than 5 picograms of Melatonin per ml of plasma would be a warning sign.

Question 9. Where can we get these patches? We have noticed that demand is already high, not just in France but also back home in England and Germany. When are you going to satisfy this demand?

We have commissioned experts to manufacture dual-compartment patches. Our objective is to have a patch ready for use by the second quarter of 2017, and to obtain a "TUA" (Temporary Use Authorisation for patients) by July 2017, after we grant licences to partner pharmaceutical laboratories, who are already interested in this issue, which represents a great economic opportunity for them.

Question 10. Is this ultimately the end of sleeping pills, anti-depressant and anti-anxiety drugs? A revolution!

Yes, that is correct, James and Alois. These new treatments, which result from the discovery of the Sleep-Wake system, should rapidly provide a promising alternative, for all the reasons mentioned above, to current treatments based on sleeping pills, anti-depressant and anti-anxiety drugs and their numerous adverse effects.

The same applies to treatments targeting neurodegenerative diseases, particularly Alzheimer's disease for which there is no effective treatment whatsoever, as acknowledged by the French National Health Authority (HAS) at the end of 2016, who advised our political leaders to remove these treatments from the list of reimbursable items. The leading trade unions followed suit and asked physicians to stop prescribing them. This brave recommendation was ignored by the Minister of Health, who is overly dependent on Big Pharma!

Question 11. So you think you can cure or prevent our two diseases?

To date, all research avenues consisting of determining the origin of the different types of brain lesion observed in the diseases named after you have been fruitless.
Logically, in order to find a preventive or curative treatment for these diseases, we need to know their causes.

In both diseases, the accumulation of amyloid-beta proteins (senile plaques), α synucleins and abnormal tau protein filaments (neurofibrillary degeneration) ultimately causes the death of neurons. This damage results from the destruction of neural protein structures by oxygenated free radicals.

Current research avenues are destined to fail as they confuse the consequences of these diseases with

their actual causes.

The discovery of the Sleep-Wake system helped us determine, in an extremely precise manner, the causes of the diseases named after you: the largely insufficient pineal secretion of the 3 hormones (Melatonin, 6-MH and Valentonin), which is perfectly correlated with the clinical symptoms.

This is why we are very optimistic about the effectiveness of the hormone replacement therapy which directly stems from this providential discovery.

Question 12. Will we see a reversal of existing lesions and disorders?

The administration of the treatments before the terminal stage should help reduce motor impairments and restore sleep, memory and mental functions in your two diseases.

With the administration of 3mg of Melatonin in the evening at bedtime, by preserving surviving neurons, we can expect, thanks to adaptive neuroplasticity, a reduction in existing neuronal damage, maybe even the appearance of new neurons.

The neurons' ability to multiply can also be counted on, i.e. their capacity to give birth to new neurons at the end of their life. It has already been proven that we can produce at least 700 new neurons every day (6).

Question 13. What other diseases will you be able to avoid or stabilise?

The two hormones of day and night regulate the body's psychic and vegetative life over the 24 hours of the sleep-wake cycle, by controlling neurophysiological processes and the secretions of all endocrine glands, the most important being the hypophysis, thyroid, adrenal glands, ovaries and testicles. Therefore they must have an impact on the development of all pathological processes.

Under these circumstances, it is legitimate to hope for numerous potential therapeutic applications of this discovery. Great opportunities await.

Question 14. Why did you give your patents to a Christian foundation?

For personal reasons linked to the circumstances of my discovery, and our spirituality, my wife Marianne and I decided to create the "Sister Josefa Menéndez" Endowment Fund.

We assigned all intellectual property rights to the patents that we registered in February 2015 to this Fund. All royalties on the sales of medicinal products collected by this endowment fund, as well as all donations collected, will go towards supporting medical and scientific research. The objective is to improve the treatment of neurological disorders at all stages of life, and all other conditions caused by the malfunction of the Sleep-Wake system.

My dear friend Pr Henri Joyeux, who I have known since 1974, as he pointed out in his Letter no. 116 of 29 April 2016 ("Sleep-Wake: A Phenomenal Discovery") joined us in July 2015. He is the Vice-President of the

Sister Josefa Menéndez Fund. We decided to combine our efforts to publicise this discovery, which is in the best interest of patients of all ages. This information will be followed by several other newsletters and videos before the end of the year.

Question 15. Which laboratory will market your discovery?

We envisage granting patent licences for these new medicinal products to several pharmaceutical laboratories, as the market potential is enormous and we wish to avoid creating a monopoly situation for a single laboratory. We initially wish to remain independent and retain control of development until the patches are ready.

Question 16. When will they be widely available?

As I just said, the definitive form of the dual-compartment patch, including the 2 doses, will be developed and manufactured in the 2nd quarter of 2017. The foundation, to which we have entrusted this mission, will then sign licence agreements with pharmaceutical laboratories to rapidly obtain a "TUA" (Temporary Use Authorisation for patients) and make the medicinal product available to patients, as early as July 2017. We will not need to provide clinical evidence by conducting phase II and III studies, as our current pharmacological knowledge of the 2 endogenous hormones, Valentonin and 6-methoxyharmalan, is sufficient to immediately place these medicinal products on the market.

This is a natural hormone replacement therapy designed to make up for the deficient secretions of the pineal gland. Administered during the secretion period, it will replicate, under physiological conditions, the secretions of the 2 hormones by the pineal gland. The absorbed doses of VLT and 6-MH after application of the patches correspond with physiological secretions; moreover, this treatment guarantees the absence of adverse effects.

Question 17. Dear colleague Jean-Bernard Fourtillan, we have seen how generous you are by entrusting all your research and patents to a spiritual foundation, the Sister Josefa Menéndez Fund. Can we recommend that the general public help speed up the process, as it is a matter of urgency for so many patients suffering from the diseases named after us?

Yes, it is possible to help us make these new treatments available to patients as soon as possible.
– By promoting and buying **the book and the brochure**: "The pineal gland and the Sleep-Wake system. Therapeutic applications"
– **Donations** made to the Sister Josefa Menéndez Endowment Fund will help us independently finance the development of the pharmaceutical forms of the patches, so they can be made available to patients as quickly as possible.
You can access regular updates on the situation, by following the news on the website.

James Parkinson and Alois Alzheimer

Post-Scriptum

On the website Fonds-sœur-josefa.org :
– Book and Brochure "The pineal gland and the Sleep-Wake system. Therapeutic applications"
– YouTube videos:
"The pineal gland and the sleep-wake system. Therapeutic applications", Pr J.B. Fourtillan (YouTube: duration 37 minutes)
"Pr JB Fourtillan answers Pr H Joyeux's questions" Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 1 hour)
"The Sleep-Wake system in Creation", Pr J.B. Fourtillan (YouTube, duration: 14min 35s + 2min 13s)
"*Les causes et le traitement de la maladie d'Alzheimer enfin découverts !* (The causes and treatment of Alzheimer's disease finally discovered) ", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 13min 30)
"*Les véritables Causes et le Traitement de la maladie de Parkinson* (The real causes and treatment of Parkinson's disease)**"**, Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 14 min 25)

Sources

(1) REM sleep follows slow sleep ("slow-wave sleep" referring to stages 3 and 4) and constitutes the fifth and final stage of a sleep cycle. One "night" consists of 3 to 6 successive cycles, each lasting 90 to 120 minutes. (according to wikipedia)
(2) Links between neurons
(3) Letter no. 136 "I, your pineal gland, aka epiphysis"
(4) Most effective medicinal product for improving motor impairments.
(5) A pharmacophore consists of the pharmacologically active part of a molecule used as a model. Pharmacophores are therefore sets of active atoms which support the pharmacological activity and are used in the design of medicinal products. (according to wikipedia)
(6) The demonstration is explained in the book *Tout savoir sur Alzheimer et Parkinson* (All you need to know about Alzheimer's and Parkinson's) – Rocher publishers, 2016