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► To cite this version:

Alexis Elbaz. In search of the causes of Parkinson's disease, seasons 1 to 4. European Journal of Epidemiology, 2011, 26 (7), pp.505-509. 10.1007/s10654-011-9587-0 . hal-00702657

HAL Id: hal-00702657

<https://hal.science/hal-00702657>

Submitted on 31 May 2012

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In search of the causes of Parkinson's disease, seasons 1 to 4

Alexis Elbaz^{1,2}

¹INSERM, U708, Neuroepidemiology, F-75013, Paris, France

²UPMC Univ Paris 06, UMR_S708, Neuroepidemiology, F-75005, Paris, France

Corresponding author

Alexis Elbaz, MD, PhD. Inserm Unit 708, Neuroepidemiology. Hôpital de la Salpêtrière. 75651 Paris Cedex 13. France. Email: alexis.elbaz@upmc.fr

A comprehensive review on the etiology and epidemiology of Parkinson's disease (PD), authored by Wirdefeldt and colleagues, is published as a separate supplement by the *European Journal of Epidemiology* [1]. The authors have undertaken an enormous task, reviewing and synthesizing evidence from over 600 references covering descriptive epidemiology, pre-symptomatic symptoms, genetic epidemiology, and several risk or protective factors of PD. This review provides an up-to-date reference guide and I am certain that it will be of interest to a wide range of scientists and largely cited by them. In another paper from this issue of the Journal, Wang and colleagues investigate the relation between Parkinson's disease and ambient exposure to pesticides in the Central Valley of California using an innovative method of exposure assessment [2].

Both papers demonstrate that the field has evolved considerably and represents an exciting area of research with a number of highlights and striking turns of events. We now live in a world in which TV series have become one of the most popular forms of entertainment. While I am certainly not a specialist (indeed, my TV has been broken for quite some time), I am unaware of any show featuring epidemiologists and geneticists as main characters. What would such a show on the continuing search for the causes of PD look like? Let's turn on the TV.

Season 1

Season 1 is set in London, England, in the XVIIIth and XIXth centuries and it tells the fascinating life of a remarkable man whose name was James Parkinson (1755-1824). With each new episode, we see Parkinson grow into a man and become involved in social and revolutionary causes. At the same time, he becomes a doctor and takes over his father's practice. In addition to numerous medical works in different areas, including gout, appendicitis, and mental health, Parkinson's major contribution is *An Essay on the Shaking Palsy* (1817) in which he establishes PD as a clinical entity and gives its classic clinical description. We then see how Parkinson progressively turns from medicine to geology and palaeontology and writes his *Organic Remains of the Former World*. Many other wonderful stories about this character are told.

One of the last episodes takes place in Paris, a few decades later, when Jean-Martin Charcot, from the Salpêtrière hospital, recognises the significance of Parkinson's work and, for the first time, calls the condition *la maladie de Parkinson*.

Unfortunately, despite wonderful actors, beautiful scenery, and historical costumes, season 1 fails to attract a large audience. In order to promote interest, the producers skip many years and, for this season's last episode, transport us to the US in the late 1970s-early 1980s. In 1976, we see a college student manufacturing 1-methyl-4-phenyl-4-propionpiperidine (MPPP), an analog of the synthetic opioid meperidine. The process goes wrong one day and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) contaminates MPPP. A few days after injecting himself with the product, he rapidly develops Parkinsonism. The next scene takes place in California (1982) where seven young addicts who also used MPPP contaminated with MPTP are diagnosed with Parkinsonism.

The producers have succeeded: as the suspense rises, the audience does too!

Season 2

In the first episode of season 2, scientists are able to determine that MPTP is the responsible agent [3]. Studies in primates are performed and show that MPTP injections result in Parkinsonism which is improved by levodopa. Scientists determine that MPTP is metabolized into MPP+, which is transported into the neurons by the dopamine transporter and has a chemical structure similar to that of paraquat, a widely used herbicide.

This major finding leads to the investigation of pesticides as potential risk factors for PD. Many case-control studies are performed and several show that farming and professional exposure to pesticides are associated with PD; findings for rural living and well-water drinking are less clear [4-6].

At the same time, another striking finding emerges. Several epidemiologic studies show that people who smoke cigarettes have a decreased risk of PD. In several episodes of this season and the following ones, this unexpected association is confirmed and meta-analyses show that there is a clear dose-response [7;8]. Researchers try to elucidate what leads to this surprising association, but, as the show progresses, it becomes clear that there is no definitive answer. Twin studies are not in favour of a genetic common cause [9;10]. Cohort studies suggest that survival bias is an unlikely explanation [11;12], and that duration, rather than intensity, of smoking is protective [13], a finding that has important implications for animal studies and clinical trials [14]. It also becomes clear that this association is present as long as 20 years before the disease starts [13]. Researchers develop alternative study designs, including assessment of passive [15] and parental smoking [16]. In addition, studies show that the activity of monoamine oxidase B, which metabolizes MPTP into MPP+, is reduced in smokers' brains [17], and that two cigarette smoke compounds, nicotine and hydroquinone, inhibit the aggregation of alpha-synuclein [18]. Over 4000 chemical compounds are created by burning a cigarette and it remains unknown whether other compounds play a role. Altogether, these findings suggest that either smoking is truly neuro-protective, although the precise biological mechanisms are not elucidated, or that reduced smoking in PD patients results from pre-symptomatic PD (reverse causation) since increasing evidence shows that non-motor symptoms may be present many years before the motor signs appear [19].

A few episodes later, we learn that coffee drinking and the daily amount of caffeine are also inversely associated with PD, independently of smoking [7]. In Singapore, black tea, which contains caffeine, is associated with reduced PD risk, while green tea, which does not contain caffeine, is not [20]. Caffeine inhibits the adenosine A2 receptor and clinical trials start investigating selective antagonists of the adenosine A2 receptor as potential PD treatments [21].

As season 2 unfolds, the identification of several environmental exposures that modify PD risk gives the audience the impression that PD is mainly due to environmental causes [22].

Hey, wait! The last episode takes place at a scientific meeting where geneticists have gathered to discuss their latest findings. Several teams have identified large families in which PD is transmitted as a Mendelian trait. Do genetic factors also play a role? The audience is left with this burning question and will have to wait until season 3.

The ratings have never been that high, Dr House makes a guest appearance, and the show wins its first international award!

Season 3

In Season 3, things pick up even more. Several episodes take place in genetic laboratories and each tells the discovery of a new PD gene. Several genes associated with Mendelian forms of the disease are identified, which has a major impact on the understanding of the mechanisms of the disease. Terms such as alpha-synuclein aggregation, mitochondrial dysfunction, oxidative stress, or proteasome inhibition are repeatedly cited. Not only are major genes discovered, but susceptibility genes associated with lower penetrance are also identified and shown to increase the risk of sporadic PD.

In parallel, several large cohorts in the US and other parts of the world have identified sufficient numbers of PD patients to investigate a wide range of exposures, such as physical activity, body mass index, dairy products, and uric acid and cholesterol level, without the limitations of case-control studies.

In season 3, we also see how an increasing number of studies find an association between PD and professional exposure to pesticides, although most lack precise exposure assessments and include few exposed subjects [6]. It becomes obvious that professional exposure to pesticides is a complex type of exposure because it entails a large variety of products that have evolved considerably over time and different types of agriculture involve different patterns of exposure (mainly due to different types, frequencies, or methods of spraying, and different types of products). Some studies, including the Agricultural Health Study (AHS) [23], a French study among farmers [24], and a collaborative European study [25], take a step further and try to investigate specific products or dose-effect relations using more precise exposure assessment tools. In parallel, toxicological studies start to develop and show that specific pesticides, such as organochlorines, rotenone, paraquat, maneb, are toxic for dopaminergic neurons and induce changes compatible with the mechanisms involved in PD [26].

Let's focus on a specific episode of season 3. We are back in California, more precisely in an agricultural region known as the Central Valley. The episode starts in a quiet orchard and the camera zooms on a beautiful orange tree. Suddenly, we hear a plane flying over the countryside and see how it sprays a cloud that progressively falls over the trees: these are the pesticides used to kill the weeds, insects, and fungi that ruin the harvests. Then, we hear the wind blowing and see how the cloud drifts from its target towards a nearby village. The next scene finds Beate Ritz, an environmental epidemiologist, in her UCLA office. While she draws circles on beautifully coloured maps, she explains the Parkinson's Gene and Environment (PEG) case-control study that aims at investigating whether people who live close (i.e., at a distance of less than 500 meters) to fields sprayed with pesticides are at higher risk of PD. The authors combine land-use data together with data from the Pesticide Use Report (PUR) system that has existed in California since 1974 and the study participants' residential addresses to assess environmental exposure to pesticides. Based on developmental animal models [27], the authors focus on paraquat and maneb (dithiocarbamate fungicide) and show that people living close to fields sprayed with both pesticides have an increased risk of PD, even after adjusting for occupational exposure. These findings have important implications since they suggest that non-occupational exposure to lower doses of pesticides may increase PD risk, therefore increasing the population attributable fraction due to pesticides if this relation was causal. In addition, this study provides evidence that genetic susceptibility may interact with pesticide exposure [28;29]; other investigators explore this new area of research [30-32], and these findings need to be replicated.

A this point, given the increasing number of studies on the relation between PD and pesticides, agribusiness companies producing pesticides start to become interested in this question, and to fund research, such as the review performed by Wirdefeldt and colleagues [1]. As season 3 becomes ever more intricate, the audience understands that the cause of PD is multifactorial and involves environmental and genetic risk or protective factors.

Several awards later, the audience increases every week and the show has its own Facebook page with millions of fans 'liking' it!

Season 4

We are now in the middle of season 4 and the action still isn't letting on. This is the era of genome-wide association studies (GWAS); the actors keep talking about microarrays, SNPs, pathways, interactions, multiple testing, and extremely small p-values. Several GWAS are published and show that in addition to two major susceptibility genes, alpha-synuclein and MAPT [33], nine other genes may be associated with sporadic PD [34].

The last episode to date highlights new findings from the AHS [35]. The authors of this study focus specifically on pesticides that induce oxidative stress or mitochondrial dysfunction, including rotenone and paraquat, and find them associated with PD. These findings suggest that different pesticides sharing similar mechanisms of action may actually play a role, rather than a single type of product, and that associations with PD may therefore not be limited to a single type of pesticides; therefore, more mechanistic studies on pesticides are needed in order to define which ones are relevant for PD and help exposure assessment. Discussions on causality should consider these recent observations as they are tightly linked to biological plausibility.

In a forthcoming episode, Anthony Wang, a student working with Ritz, presents new findings from the PEG study published in this issue of the Journal [2]. This paper investigates ambient exposure to maneb and paraquat based on both residential and occupational addresses, and ziram, another dithiocarbamate fungicide that causes dopaminergic neuron damage in cell culture, is added to the analysis. Except for paraquat, few subjects are exposed to only one of the pesticides, which makes the assessment of their individual effects difficult. The main finding of this paper is that combined exposure to the three pesticides is strongly associated with PD. Pesticides are usually sprayed during working hours: an important strength of the study is that it investigates whether persons who work near fields sprayed with pesticides are at higher risk of PD. The study shows stronger associations for ambient workplace exposure than for residential exposure, thus suggesting that ambient workplace exposure should not be overlooked; it is unclear, however, to what extent working in farms plays a role. Stronger associations are observed for persons younger than 60 years than for older people; the interpretation of this difference is not straightforward since the PUR system exists since 1974 and exposures that may have been relevant for older persons are not included. In this study, combined exposure does not necessarily mean exposures occurring at the same time; one important implication is that not only different pesticides may play a role as discussed above, but also the effects of pesticides involving different mechanisms may accumulate, in agreement with a multiple-hit hypothesis.

The GIS-based exposure assessment method developed by the authors represents an important improvement over studies based on self-report and it allows to investigate a wide-range of specific products. This study is the first to implicate ziram, an inhibitor of the ubiquitin-proteasome system, in PD. There are, however, hundreds of pesticides that are often used in conjunction and teasing out their independent effect is likely to be unrealistic. Obviously, the authors need to make a selection of candidate pesticides and they reasonably use prior knowledge for that purpose. Unfortunately, data on the effects of many pesticides in humans and animals remain limited, and it is therefore possible that there may be some degree of confounding; for instance, effect estimates decrease (but remain significant) after adjustment for organochlorine and organophosphate insecticides. Altogether, this study, through the implementation of an innovative method of exposure assessment, makes an important contribution on the role of ambient workplace and residential exposure in PD, and replication of the findings on ziram is needed.

Keep watching

What will happen next? Creative approaches, including detailed exposure assessment methods such as those developed by Ritz's team, will be required. Sophisticated statistical methods will be needed to analyze multiple correlated exposures and genes and their interactions in large samples. Hopefully, we will see more collaboration between researchers from different fields and we hope to see more toxicologists in the show.

Ideally, these findings will translate into medical practice and help to alleviate PD symptoms, slow PD progression, and even prevent PD. There are, however, still many difficulties and Wirdefeldt and colleagues conclude: "Hence, our hopes to control PD through primary intervention in the foreseeable future are not high" [1].

The show will run and run: keep watching!

Acknowledgments

I thank Hilary Boys, Frédéric Moisan, Marie Vidailhet, and Elisabeth Vincentelli for helpful comments.

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